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OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

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This document provides the HED's human health risk assessment for the Registration Review of Ethoprop [*S,S*-dipropyl *O*-ethyl phosphorodithioate]. The occupational and residential exposure assessment/risk assessment were provided by Matthew Lloyd (RAB57); the residue chemistry assessment and dietary exposure assessments were provided by Katelynn King (RAB57); and the hazard characterization and endpoint selection was provided by John Liccione (RAB57).

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1.0 Executive Summary

Background

Ethoprop [*S,S*-dipropyl *O*-ethyl phosphorodithioate] is an organophosphate (OP) insecticide/nematicide currently registered as an emulsifiable concentrate (EC) and two granular formulations (15% and 20% ai) for use on various agricultural crops. The end use products are applied in the field using ground and soil incorporated equipment once early in the season (typically pre-plant). All the available products are classified as Restricted Use and may be purchased and used only by certified applicators or persons under their direct supervision. The currently registered application rates for ethoprop generally range from 3 lbs ai/A to 12 lbs ai/A via ground application. The applications are specified to be conducted with closed systems, with the exception of backpack granular application for bananas.

Based on the registered use sites, humans may be exposed to ethoprop in food and drinking water since ethoprop may be applied directly to growing crops and application may result in ethoprop reaching surface and ground water sources of drinking water. Dermal and inhalation exposures are anticipated for occupational handlers. There are currently no registered residential uses of ethoprop. There is the potential for non-occupational exposure as a result of spray drift and ambient bystander exposure.

Hazard Assessment

Ethoprop is a member of the OP class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for ethoprop involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For ethoprop, AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Ethoprop, unlike some other OPs, does not require metabolic activation to the oxon metabolite to inhibit AChE (i.e., the parent compound is the active form inhibiting AChE). OPs also exhibit a phenomenon known as steady-state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. In the case of ethoprop, the results show a clear pattern of steady state reached within two weeks of exposure. As such, endpoint selection is identified for the acute, single day effects and steady state effects. For the purposes of the occupational risk assessment, only the steady-state duration is relevant to the exposure scenarios. For the purposes of the non-occupational risk assessments, the acute and steady-state durations are relevant to the exposure scenarios.

The toxicology database for ethoprop is considered adequate for risk assessment. There are acceptable studies available for toxicity endpoint selection. Ethoprop has dose-response data across multiple lifestages, durations, and routes for both red blood cell (RBC) and brain AChE inhibition. Dermal, oral, and inhalation studies allow for route-specific evaluation. There are two separate steady-state dermal PODs selected for the liquid and granular formulations of ethoprop, although both are based on red blood cell (RBC) cholinesterase inhibition. Clinical signs of neurotoxicity related to inhibition of AChE by ethoprop have been noted at higher doses in a number of studies. The CCA acute and repeated dose studies suggest quantitative sensitivity to ethoprop with respect to RBC AChE inhibition. Additionally, the Food Quality Protection Act

(FQPA) Safety Factor (SF) has been retained for infants, children, youth, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4). For all exposure scenarios, interspecies (10X) and intraspecies (10X) uncertainty factors were applied. As a result, a total uncertainty factor of 1,000X was applied for all non-cancer exposure scenarios, except dietary exposures for the adult population subgroup 50-99 years old where the FQPA SF does not apply (total uncertainty factor = 100X) and inhalation exposures where the interspecies uncertainty factor has been reduced to 3X (total uncertainty factor = 300X).

Ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. A quantitative cancer risk assessment is required (dietary and occupational handler); the Q_1* for ethoprop is 2.81×10^{-2} mg/kg/day^{-1}.

Dietary (Food and Water) Exposure and Risk The existing residue chemistry database for ethoprop is adequate for risk assessment purposes. An unrefined acute dietary exposure assessment was conducted to estimate the dietary exposure and risk associated with Registration Review. Because food and water dietary risk assessments exceed 100% of their respective population adjusted doses (aPAD & ssPAD), a combined dietary assessment was not completed. The acute dietary exposure assessment incorporated tolerance level residues, DEEM default processing factors, and 100% crop treated (PCT). The most conservative exposure model was used to assess the contributions from drinking water and the Estimated Drinking Water Concentrations (EDWCs) used PRZM-GW. The acute aggregate dietary (food only + drinking water only) exposure estimates are above HED's level of concern [>100% the acute population adjusted dose (aPAD)] for the U.S. population and all population subgroups[1]. Dietary exposure from food only at the 95th percentile of exposure is 260% of the aPAD for the U.S. population and 630% of the aPAD for all infants (<1 year old), the highest exposed population subgroup. Dietary exposure from drinking water only at the 95th percentile of exposure is 3,200% of the aPAD for the U.S. population and >10,000% of the aPAD for all infants (<1 year old), the highest exposed population subgroup.

The DEEM acute module was used to conduct refined steady-state assessments using the steady-state endpoint, two-day average dietary exposure, and 21-day rolling water averages. EFED provided daily time-series outputs that simulate 29 years of residues of ethoprop in the drinking water application scenario. This distribution was used as a residue distribution file (RDF) in DEEM for direct, all sources and indirect, all sources. For the steady-state aggregate assessment, the unrefined *food alone* and water alone exposure estimates are well above HED's level of concern for the U.S. population and all population subgroups at the 95th percentile of exposure[1]. At the 95th percentile of exposure, all infants (<1 year old) are the highest exposed subpopulation at >10,000% of the steady-state population adjusted dose (ssPAD) for the drinking water only dietary assessments.

In the case of ethoprop, a dietary cancer risk for food and drinking water together (i.e., the aggregate cancer dietary assessment) was not completed because even though the *food only* cancer risk estimate could be refined, the *water only* cancer risk estimate drives the dietary cancer risk estimation. Refinements of the *water only* cancer risk estimates are not available at

[1] Except adults 50-99 years old (acute & steady-state, *food only*)

this time. Applying the ethoprop Q1* of 0.0281 $(mg/kg/day)^{-1}$, the cancer risk estimate for the U.S. general population is 7×10^{-6} for *food alone* (based on incorporated tolerance level residues, DEEM default processing factors, and 100% crop treated (PCT)) and 5×10^{-5} for water only.

Residential (Non-Occupational) Exposure and Risk
There are currently no registered residential uses of ethoprop; therefore, a quantitative residential assessment was not conducted.

Bystander Inhalation
The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for ethoprop utilizing the currently available inhalation toxicity and air monitoring data. No risk estimates of concern were identified for either the single day or steady state analysis.

Spray Drift
A quantitative non-occupational spray drift assessment was conducted for the registered uses of ethoprop based on the emulsifiable concentrate formulation[2]. HED believes a quantitative spray drift assessment is applicable only for pre-plant groundboom soil-directed spray applications. Risk estimates related to spray drift are of concern at various distances from the edge of the field for adults and children (1 to <2 years) depending on the spray drift scenario. For adults, the screening level scenario of a high boom and fine to medium/coarse spray requires a distance of over 300 feet to reach a dermal margin of exposure (MOE) $\geq$ 1000. For children, the screening level scenario also requires a distance of over 300 feet to reach a combined (dermal and incidental oral) MOE $\geq$1000. Drift reduction technologies, such as using coarser sprays can reduce risk concerns; however, there are still risk estimates of concern at the field edge regardless of the drift scenario assessed.

Occupational Exposure and Risk
Occupational handler non-cancer dermal and inhalation exposure and risk estimates were calculated for the registered uses of ethoprop. Occupational handler risk estimates were evaluated for ethoprop based on both unit exposure data (chemical-specific and surrogate data) and available biomonitoring data. For the unit exposure data approach, risk estimates for the emulsifiable concentrate (EC) and granular (G) formulations are calculated separately because different dermal PODs were selected according to formulation type. In both cases, mixer/loader scenarios drive the occupational non-cancer risk and the level of concern (LOC) for the combined risk estimates are MOEs < 1,000. All combined (dermal + inhalation) risk estimates are of concern using label-defined engineering controls for occupational handler mixer/loaders, loaders, and applicators. For mixer/loaders using the label-defined engineering controls, total MOEs (dermal + inhalation) range from <1-11 for the liquid formulation and 19-190 for the granular formulation.

HED also evaluated the potential exposure to ethoprop using urinary concentrations of M1 (O-ethyl-S-propylphosphorothioate), as an exposure biomarker in an available observational biomonitoring study. While the individual results varied widely, non-cancer risk estimates derived from the biomonitoring study result in risk estimates of concern (i.e, MOEs below the LOC of 1,000) for mixer/loaders, applicators, and workers who conducted all three tasks. Results from the biomonitoring study are most applicable to crops/conditions in the Pacific Northwest

[2] [EPA Reg. No. 5481-9041]

because of the additional personal protective equipment (PPE) that study participants wore. As the original biomonitoring study occurred in a large portion of the occupational handler group for ethoprop occupational handlers in a discrete geographic location, there is uncertainty bridging the use of the data to other occupational handler groups with different agricultural practices and geographic variations.

HED also conducted a quantitative occupational handler cancer risk assessment using surrogate unit exposure data and a screening assessment based on the available biomonitoring data. Using the surrogate unit exposure approach, the cancer risk estimates representing label-defined engineering controls range from 10^{-4} to 10^{-6} depending on the formulation (granular versus emulsifiable concentrate) and application parameters regarding "private" versus "commercial" handlers (differ in terms of days/year of exposure). Quantitative cancer risk estimates were also calculated based on the available biomonitoring data. Those cancer risk estimates reflect engineering controls plus the use of extensive dermal PPE common in the Pacific Northwest. For those scenarios, the cancer risk estimates range from 10^{-4} to 10^{-6} depending on the application parameters around "private" versus "commercial" handlers.

A quantitative post-application non-cancer dermal exposure assessment has not been conducted for ethoprop because ethoprop is typically applied pre-plant/pre-emergent in the growing season. The REI on the currently registered labels (48 hours [and 72 hours in areas that receive less than 25 inches of rain per year]) meets the minimum requirements of the Worker Protection Standard based on active ingredients that are classified as Toxicity Category I for acute dermal, eye irritation, or primary skin irritation.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for ethoprop at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for ethoprop.

Environmental Justice:
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[3]".

Human Studies Review:
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Residential SOPs (Turf/Incidental Oral SOP), other registrant-submitted exposure monitoring studies (MRID 45621501), are: (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[4].

[3] http://epa.gov/compliance/ej/resources/policy/exec_order_12898.pdf
[4] http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html

2.0 HED Recommendations

2.1 Data Deficiencies

There are no data deficiencies for the Registration Review eligibility of ethoprop.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The FDA PESTDATA database indicates that ethoprop is completely recovered using FDA Multiresidue Protocol D (PAM I Section 232.4) and partially recovered using FDA Multiresidue Protocol E for non-oily matrices (PAM I Section 211.1). Recovery of ethoprop using Protocol E for oily matrices (PAM I Section 212.1) is small. The registrant has submitted data pertaining to the recovery of Metabolite IV through FDA Multiresidue Protocols, and these data have been forwarded to the FDA for review (03/27/1998, J. Abbotts, D239294).

2.2.2 International Harmonization

U.S. permanent tolerances are summarized in Appendix E along with International Maximum Residue Limits (MRLs) established by Codex Alimentarius Commission. Mexico adopts the U.S. tolerances and/or Codex MRLs for its export purposes. At this time the following Canada tolerances (0.09 ppm) have been used in place of the US tolerances for harmonization purposes: *bean, lima* and *bean, snap, succulent*. The following Codex tolerances (0.05 ppm) have been used in place of the US tolerances for harmonization purposes; potato and sweet potato root. Cucumber tolerances for the US and Canada are both equal at 0.02 ppm however, the Codex tolerances is at 0.01 ppm. Even though new tolerances are being recommended for harmonization, the established tolerances (as identified in Table 2.2.3.1) were used in the dietary assessment as residues.

2.2.3 Revisions to Established Tolerances

No revisions to established tolerances are required at this time. A tolerance summary for ethoprop is provided in Table 2.2.3.1.

Table 2.2.3.1. Tolerance Summary for Ethoprop

Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Banana	0.02	0.02	N/A
Bean, lima	0.02	0.09	HED recommends a tolerance change for harmonization with the Canadian tolerance.

Bean, snap, succulent	0.02	0.09	HED recommends a tolerance change for harmonization with the Canadian tolerance.
Cabbage	0.02	0.02	N/A
Corn, field, forage	0.02	0.02	N/A
Corn, field, grain	0.02	0.02	N/A
Corn, field, stover	0.02	0.02	N/A
Corn, sweet, forage	0.02	0.02	N/A
Corn, sweet, kernel plus cob with husks removed	0.02	0.02	N/A
Corn, sweet, stover	0.02	0.02	N/A
Cucumber	0.02	0.02	N/A
Hop, dried cones	0.02	0.02	N/A
Peppermint, tops	0.02	0.02	N/A
Pineapple[5]	0.02	0.02	N/A
Potato	0.02	0.05	HED recommends a tolerance change for harmonization with the Codex tolerance.
Spearmint, tops	0.02	0.02	N/A
Sugarcane, cane	0.02	0.02	N/A
Sweet potato, roots	0.02	0.05	HED recommends a tolerance change for harmonization with the Codex tolerance.

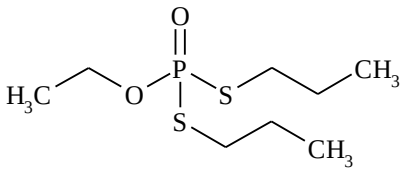
2.3 Label Recommendations

No label recommendations have been identified. A summary of the risk estimates has been provided, and shows that there are risk estimates of concern for registered uses of ethoprop based on the use information and label-required engineering controls.

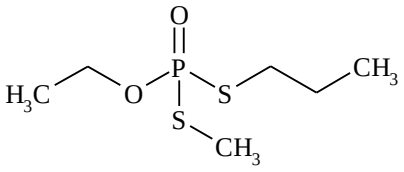
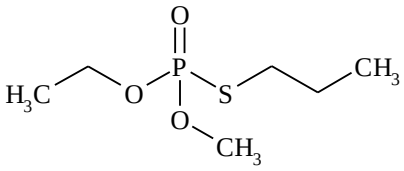
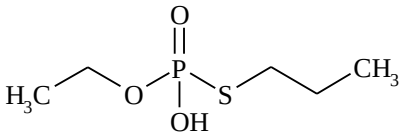
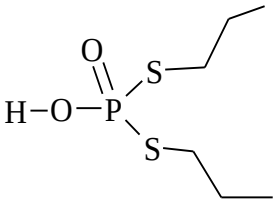
3.0 Introduction

3.1 Chemical Identity

Table 3.1. Nomenclature of Ethoprop and its Metabolites of Concern.

Ethoprop or Ethoprophos *O*-ethyl-*S*,*S*-dipropyl phosphorodithioate CAS: 13194-48-4	

[5] There are no U.S. registrations as of July 23, 2009, except for existing stocks bearing old labeling whose sale, distribution, and use is allowed, provided it is consistent with the terms of the cancellation order of July 9, 2009; *i.e.*, the EPA will allow the technical registrant to continue to sell and distribute existing stocks of the amended registered product bearing old labeling for use on pineapple for 18 months (until January 9, 2011) and persons other than the registrant may continue to sell and/or use existing stocks of product bearing the old labeling until such stocks are exhausted, provided that such use is consistent with the terms of the previously approved labeling on, or that accompanied, the modified product.

Table 3.1. Nomenclature of Ethoprop and its Metabolites of Concern.	
Metabolite II (S-Me) *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate	
Metabolite III (O-Me) *O*-ethyl-*O*-methyl-*S*-propyl phosphorodithioate	
Metabolite IV (M-1) *O*-ethyl-*S*-propyl phosphorodithioate	
SSDP (S,S-dipropyl degradate) S,S-dipropylphosphorodithioate	

S-Me, O-Me, and M-1 are all plant and animal metabolites and are also environmental degradates detectable in water. SSDP is an environmental degradate but is not a plant or animal metabolite.

S-Me and O-Me are AChE inhibitors and are therefore of concern for non-cancer risk assessments. M-1 and SSDP are not AChE inhibitors and are not of concern for non-cancer risk assessments. All four metabolite/degradates should be included in cancer risk assessments.

3.2 Physical/Chemical Characteristics

Ethoprop (O-ethyl S,S-dipropyl phosphorodithioate) is a colorless to yellow tinted liquid with a strong mercaptan odor and a boiling point of 86-91^{o} C at 0.2 mm Hg. Ethoprop is only slightly soluble in water (843 ppm at 21 C), but is soluble in most organic solvents (hexane, xylene, acetone, and ethanol). Ethoprop has a low vapor pressure (4.6 x 10^{-2} Pa). A summary of physical/chemical properties for ethoprop can be found in Appendix D.

3.3 Pesticide Use Pattern

Ethoprop is an organophosphate insecticide/nematicide currently registered as an emulsifiable concentrate (EC) and two granular formulations (15% and 20% ai) for use on various agricultural crops. Ethoprop products are classified as Restricted Use Pesticide (RUP) and may be purchased

and used only by certified applicators (or persons under their direct supervision). The end use products are applied in the field using ground and soil incorporated equipment early in the season (typically pre-plant). This application procedure is independent of the formulation. For some crops, only banded (not broadcast) applications are permitted. This restriction applies to the EC formulation for cabbage, and the EC and granular formulations for sweet potatoes. The EC formulation of ethoprop may also be applied by chemigation. Airblast, aerial, and handheld applications are prohibited on the existing registered labels (with the exception of a backpack granular application for bananas). There are no registered residential products that could be used by homeowners. With the exception of the granular application to bananas, all use patterns require engineering controls on the registered product labels. The loader/applicator scenario for bananas involves backpack application of the 15G product and requires coveralls over long-sleeve shirt and long pants, chemical-resistant gloves, chemical-resistant footwear plus socks, and a non-powered air-purifying respirator equipped with an N, R, or P-series filter.
The label requires a REI of 48 hours (72 hours in areas where rainfall is less than 25 inches per year).

Table 3.3.1. Summary of Directions for Use of Ethoprop.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Field Grown Ornamental						
Pre-plant	5481-09041 [EC]	3	1	Same as single app. rate	Not listed	CA, OR, WA only; Preplant broadcast only; Immediately incorporate to a depth of 2-4 inches
Hops						
Pre-plant During season (after pruning, before stringing)	5481-09041 [EC]	3	1	Same as single app. rate	90	Apply via chemigation, banded or broadcast application; soil incorporate 2-4 inches or water in
Tobacco						
At plant Up to 1 week	5481-09040 [15G]	6	1	Same as single app. Rate	Not listed	Apply via banded or broadcast application; Mix in top 2-4 inches of soil
Beans, succulent (snap & lima)						
At plant Up to 3 days pre-plant	5481-09040 [15G]	8.1	1	Same as single app. Rate	Not listed	Apply via banded or broadcast application
Cabbage						
At plant Up to 1 week pre-plant	5481-09040 [15G]	5.1	1	Same as single app. Rate	Not listed	Apply via banded or broadcast application
At plant	5481-09041 [EC]	5.1	1	Same as single app. Rate	Not listed	Apply via banded application; CA only
Cucumber						

Table 3.3.1. Summary of Directions for Use of Ethoprop.						
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
At plant	5481-09040 [15G]	1.95	1	Same as single app. Rate	Not listed	Apply via banded application; do not allow granules to contact seed
Corn, Field & Corn, Sweet						
At plant Pre-plant	5481-09040 [15G]	1-3 rootworms/wire worms 1.5-6	1	Same as single app. Rate	Not listed	Apply as broadcast or banded application; soil incorporate
Mint						
pre-plant or post-season	5481-09040 [15G]	3-6 lbs ai/A	1	Same as single app. Rate	Not listed	Broadcast & soil incorporate/irrigate
Pre-plant After last harvest	5481-09041 [EC]	3-6 lbs ai/A	1	Same as single app. Rate	225	Broadcast; soil incorporate 2-4 inches or water-in via irrigation
Potato (East)						
Prior to plant/At plant/pre-emergence	5481-09040 [15G] 5481-09041 [EC]	4-6 (symphylans/wire worms) 6-9 (nematodes)	1	Same as single app. rate	Not listed	Apply via broadcast or banded application; Soil incorporate after either app. Method – 2-4 inches
Potatoes (West)						
Prior to plant/At plant/pre-emergence	5481-09040 [15G]	4-6 (symphylans/wire worms) 6-12 (nematodes)	1	Same as single app. rate	Not listed	Apply via broadcast or banded application; Soil incorporate after either app. Method – 2-4 inches
Prior to plant/At plant/pre-emergence	5481-09041 [EC]	4-6 (symphylans/wire worms) 6-12 (nematodes)	1	Same as single app. rate	Not listed	Apply via broadcast or banded application; Soil incorporate after either app. Method – 2-4 inches
Sugarcane						
At planting	5481-09040 [15G]	5.88	1	5.88	Not listed	Apply via banded application; Workers doing hand planting apps or other direct contact activities

Table 3.3.1. Summary of Directions for Use of Ethoprop.						
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/A)**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
						cannot be present with 100 ft. of application equipment
At planting	5481-09042 [20G]	5.88	1	5.88	Not listed	Apply via banded application; mix in top 2-4 inches of soil Workers doing hand planting apps or other direct contact activities cannot be present with 100 ft. of application equipment
Sweet Potato						
2-3 weeks before plant	5481-09040 [15G]	3-3.9	1	3.9	Not listed	Apply via broadcast or soil band treatment; Soil incorporate w/ mechanical equipment
2-3 weeks before plant	5481-09041 [EC]	3-3.9	1	3.9	Not listed	Apply via soil band treatment; Soil incorporate w/ mechanical equipment
Banana						
Granule backpack application	5481-09040 [15G]	40 grams 15G product per ¾ meter radius around base of tree	2	(121 lbs ai/A based on typical area treated for backpack spreaders)	Not listed	Evenly apply granules; soil incorporate by hand raking

1 – Ethoprop rate information expressed in this document as lbs ai/A; many crop application rates are also expressed in a rate/linear foot.
2 – EC = Emulsifiable Concentrate; G = Granular

3.4 Anticipated Exposure Pathways

Humans may be exposed to ethoprop in food and drinking water since ethoprop may be applied directly to growing crops and application may result in ethoprop reaching surface and ground water sources of drinking water. There are no residential uses of ethoprop. There is the potential for non-occupational exposure as a result of spray drift (via the dermal and incidental oral routes of exposure) and ambient inhalation exposure as a result of agricultural applications. Based on the registered use pattern for ethoprop, steady-state dermal and inhalation exposures are anticipated for occupational handlers.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[6]." As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Ethoprop is a member of the OP class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/ mode of action (MOA), for ethoprop involves inhibition of the enzyme AChE via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system (see Figure 1). For ethoprop, AChE inhibition is the most sensitive endpoint in the toxicology database across multiple species, durations, lifestages, and routes. AChE inhibition is the focus of this hazard characterization; the availability of reliable AChE inhibition dose response data is one of the key determinants in evaluating the toxicology database.

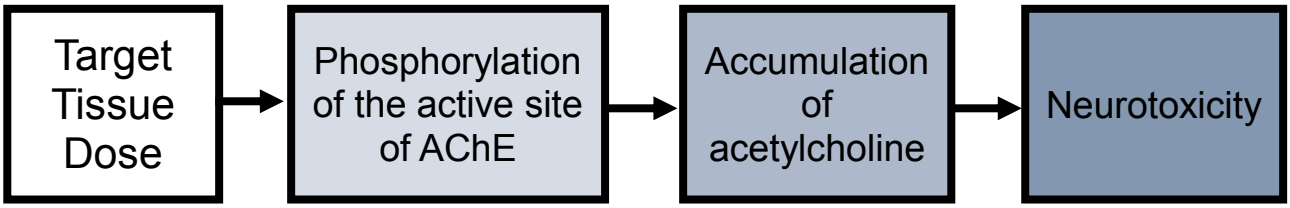


Figure 1. Adverse Outcome Pathway for OPs.

Consistent with risk assessments for other AChE-inhibiting compounds, OPP has used a benchmark response (BMR) level of 10% and has thus calculated BMD_{10}'s and $BMDL_{10}$'s (see

[6] Available: (http://epa.gov/compliance/ej/resources/policy/exec_order_12898.pdf

Appendix 1 for summary of OPP's AChE policy). The BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}. As a matter of science policy, the agency uses the BMDL, not the BMD, for use as the POD (USEPA, 2012). All BMD/BMDL modeling for all individual datasets was completed using USEPA BMD Software, version 2.2 and an exponential model was used to fit the data. Summary tables of the BMD analyses can be found in Appendix B.

4.1 Toxicology Studies Available for Analysis

The toxicology database for ethoprop is complete for risk assessment. There are acceptable studies available for toxicity endpoint selection; they include:

- subchronic oral toxicity study in the dog
- chronic oral toxicity studies in rats and dogs
- carcinogenicity studies in rats and mice
- developmental studies in rats and rabbits
- reproduction study in rats
- acute and subchronic neurotoxicity studies in rats
- developmental neurotoxicity (DNT) study in rats
- acute and repeated comparative cholinesterase AChE studies in juvenile and adult rats
- delayed neurotoxicity study in hens
- subchronic dermal toxicity in rats and rabbits
- repeated dosing inhalation studies in rats
- immunotoxicity study in rats
- complete mutagenicity study battery
- metabolism study in rats

4.2 Absorption, Distribution, Metabolism, & Excretion (ADME)

Ethoprop, unlike some other OPs, does not require metabolic activation to the oxon metabolite to inhibit AChE. In a metabolism study, ethoprop was administered to Crl:CD(SD)BR rats as a single IV bolus (males and females); single oral bolus (females, metabolism and pharmacokinetic studies; males, metabolism only); or by multiple oral doses (MRID 41804301). Oral absorption of ethoprop is rapid and essentially complete by 48 hours. The principal route of excretion was in urine (>50% of dose). Radioactivity was also found in feces (7-16%) and respiratory air (11-19%). Terminal elimination half-life in blood was 92-135 hours. Metabolism was by dealkylation of one or both S-propyl groups, followed by hydroxylation and conjugation. The main urinary metabolites were *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate (SME), *O*-ethyl-*O*-methyl-*S*-propyl phosphorodithioate (OME), and *O*-ethyl-*S*-propyl phosphorodithioate (M1). .

4.2.1 Dermal Absorption

No dermal absorption study is available for ethoprop. A dermal absorption factor is not required since PODs for dermal exposure were selected from route-specific dermal toxicity studies

for both the liquid and granular formulations. These dermal toxicity studies provided quality AChE inhibition data, which were evaluated using BMD modeling techniques and are being used for dermal risk assessment (see Section 4.5).

4.3 Toxicological Effects

Ethoprop has dose-response data across multiple lifestages, durations, and routes for both RBC and brain AChE inhibition. Many of these studies have been evaluated with BMD techniques. However, it should be noted that some of the data did not model well, and these data did not have BMD values that could be used in the risk assessment. The CCA studies (acute and repeat phases), which were conducted at time to peak inhibition (24 hours – adults; 8 hours – pups), provided the best data to examine temporality. Studies conducted by the dietary routes of exposure, e.g., the SCN and DNT studies, did not report when AChE activity was measured, so it is not certain if measurements were performed consistently (at the same time of day) within a study. The ACN study reported that measurements were done at time to peak inhibition, however, no adequate fits were obtained with either brain or RBC AChE data from this study because of dose spacing issues.

Signs of neurotoxicity related to inhibition of AChE by ethoprop have been noted at higher doses in a number of studies. In the ACN study, salivation, lip smacking, ataxia, negative pupillary response and/or tremors were noted at 25 mg/kg. At doses > 25 mg/kg, the incidence and frequency of these signs increased and, in addition, negative corneal response, negative air drop reflex, negative startle response, increased latency until first step, paralytic gait abnormalities, reduced activity, prostration and labored or gasping respiration were observed. Decreased hindlimb grip strength, motor activity and analgesic response time were noted in the SCN study (LOAEL = 27 mg/kg/day; the NOAEL = 2.6 mg/kg/day). For the DNT study, the maternal LOAEL for ethoprop in rats was 180 ppm (38.2 mg/kg/day during lactation) based on clinical signs (coarse tremors, repetitive chewing, muscle fasciculations). The PoDs selected are protective of these clinical signs. There were no clinical signs of toxicity in the CCA repeat study in adults and PND11 pups administered doses up to 1 mg/kg/day. Hen studies were negative for indications of organophosphate induced delayed neuropathy.

The CCA acute and repeated dose studies suggest quantitative sensitivity to ethoprop with respect to RBC AChE inhibition. In both the CCA acute single-dose and repeat-dose studies, there was no apparent dose-response in adults with respect to ethoprop administration and brain AChE inhibition, whereas this was not the case for PND11 pups. BMD values were obtained for pups based on the dose response brain AChE inhibition data. With respect to RBC AChE inhibition, pups were also more sensitive than the adults. There is confidence in the design of the CCA studies in that time to peak inhibition for both adults and pups were established. In the CCA studies, AChE measurements were performed at time to peak effect for adults (24 hours) and pups (8 hours). A gestational component was not included in the CCA study, but included in the DNT studies (discussed below).

In the DNT definitive study, the dams were more sensitive than PND 21 pups to RBC AChE inhibition. In the range-finding DNT study, the dams were also more sensitive than gestation day 20 (GD20) fetus to RBC AChE inhibition. The DNT studies were conducted by the dietary

route of exposure, and it is difficult to relate the results to time to peak effect (which the CCA studies indicated a significant difference between adults and pups).

Ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. The Q_1* for ethoprop is 2.81×10^{-2} mg/kg/day^{-1}.

The acute toxicity data for ethoprop show that ethoprop has a high acute toxicity category for acute oral and acute inhalation toxicity (Category I/II, respectively). It is a Toxicity Category I/II for acute dermal toxicity, depending on the study. The data show severe acute eye irritation (Category I) and is a strong dermal irritant (Category I).

4.3.1 Critical Durations of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. One advantage of an AOP understanding is that human health risk assessments can be refined, and focused on the most relevant durations of exposure. The following text provides an analysis of the temporal pattern of AChE inhibition from acute, single dosing and repeated dosing studies in laboratory animals for ethoprop. This analysis provides the basis for determining which exposure durations are appropriate for assessing human health risk. Tables 4.3.1.1 and 4.3.1.2 provide a summary of the selected results from experimental toxicology studies with ethoprop. The high quality, well-designed CCA studies (acute and repeat phases), which were conducted at time to peak inhibition, provided the best data to examine temporality. The CCA studies revealed significant differences in the time to peak inhibition between adults (24 hours) and pups (8 hours). Some of the data sets from other studies (e.g., ACN and reproductive toxicity studies) did not model well or were less reliable for various reasons (low number of animals; questionable model variance; and dose spacing issues).

Table 4.3.1.1 –Ethoprop BMD_{10} Results (mg/kg/day) for Brain and RBC AChE Inhibition Over Time in Male and Female Adult Rats

Days of dosing	BMD_{10} - RBC		BMD_{10} - Brain	
	Males	**Females**	**Males**	**Females**
1[a]	0.649	1.095	no dose response	no dose response
11[b]	0.553	0.247	no dose response	no dose response
14[c]	not applicable	0.164	not applicable	2.411
28[d]	0.238	0.454	not measured	not measured
37[e]	not applicable	0.252	not applicable	5.012

[a] MRID 46278701 CCA Acute Study – Single Dose (Adults)
[b] MRID 46636401 CCA Repeat Study – Repeat Dose
[c] MRID 46364802 RF DNT study (Dams treated GD6 – GD20)
[d] MRID 45388502 28-day oral study in the rat
[e] MRID 46364801 Developmental Neurotoxicity Study (LD 21 dams); maternal rats exposed from GD 6 through 21 days and 21 days during lactation.

Table 4.3.1.2 –Ethoprop BMD_{10} Results (mg/kg/day) for Brain and RBC AChE Inhibition Over Time in Male and Female Pup Rats				
Days of dosing	**RBC**		**Brain**	
	Males	**Females**	**Males**	**Females**
1[a]	0.570	0.549	0.962	0.817
11[b]	0.106	0.154	0.187	0.151

[a] MRID 46278701 CCA Acute Study – Single Dose (Adults)

[b] MRID 46636401 CCA Repeat Study – Repeat Dose

As shown in Tables 4.3.1.1 and 4.3.1.2, the BMD values for adult and pup RBC were highest after a single oral dose (CCA acute study) and were lower after repeated exposures within these populations. RBC AChE inhibition was similar (0.549 – 1.095 mg/kg/day) for adults and pups following acute (single oral) exposure. RBC AChE inhibition was also comparable (0.106 – 0.553 mg/kg/day) for adults and pups after repeated oral dosing. In comparing compartments, RBC AChE inhibition in adults was more sensitive than brain AChE inhibition in this population. For the pups, there was slight sensitivity between the compartments after a single dose but not with 11 days of dosing. The definitive and the range-finding DNT dietary exposure studies yielded BMD_{10} values of 5.012 mg/kg/day (lactational day 20 dams) and 2.411 mg/kg/day (GD20 dams), respectively. Studies for the dermal and inhalation routes in adult animals allow for route-specific evaluations. For the dermal and inhalation studies, RBC and brain AChE inhibition were comparable.

OPs exhibit a biological response known as steady state AChE inhibition. After repeated dosing at the same dose level, the degree of inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChE inhibition at a given dose remains consistent across duration. In general, OPs reach steady state within 2-3 weeks but this can vary among OPs. In the case of ethoprop, the results in Tables 4.3.1.1 and 4.3.1.2 indicate that steady state may be reached by 11 ─ 14 days of exposure. Given the results in Tables 4.3.1.1 and 4.3.1.2, for ethoprop, acute (single day) and steady state durations are appropriate for human health risk assessment. As such, endpoint selection discussed below focuses on acute, single day effects and steady state effects.

Although there are rat data at a shorter time period (i.e., 11 days) than 21 days, exposure assessments of 21 days and longer will be conducted for all routes of exposure (i.e., oral, dermal and inhalation) for all single chemical OP assessments. Although the durations of the toxicity and exposure assessments may differ, an exact match is not necessary and would suggest a level of precision that the toxicity data do not support. Given this, the 21-day and longer exposure assessment is scientifically supportable and also provides consistency with the OP cumulative risk assessment across the OPs.

4.4 Literature Review on Neurodevelopment Effects

For the OPs, historically the Agency has used inhibition of AChE as the POD for human health risk assessment; at present time, this policy continues. This science policy is based on decades

of work which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity. The use of AChE inhibition data for deriving PODs was supported by the FIFRA SAP (2008, 2012) for chlorpyrifos as the most robust source of dose-response data for extrapolating risk and is the source of data for PODs for ethoprop. A detailed review of the epidemiological studies used in this review can be found either in the 2014 chlorpyrifos revised draft human health risk assessment (D424485, D. Drew et al, 12/29/2014) or in the 2015 literature review for other organophosphates (OPP/USEPA; D331251; 9/15/15).

Newer lines of research on OPs in the areas of potential AOPs, *in vivo* animal studies, and notably epidemiological studies in mothers and children, have raised some uncertainty about the agency's risk assessment approach with regard to the potential for neurodevelopmental effects in fetuses and children. Many of these studies have been the subject of review by the agency over the last several years as part of efforts to develop a risk assessment for chlorpyrifos (D424485, D. Drew et al, 12/29/2014). Initially, the agency focused on studies from three US cohorts: 1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children's Center for Environmental Health (CCCEH) at Columbia University; 2) the Mt. Sinai Inner-City Toxicants, Child Growth and Development Study or the "Mt. Sinai Child Growth and Development Study;" and 3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. The agency has evaluated these studies and sought external peer review (FIFRA SAP reviews in 2008 and 2012; federal panel, 2013[7]) and concludes they are of high quality. In the three US epidemiology cohort studies, mother-infant pairs were recruited for the purpose of studying the potential health effects of environmental exposures during pregnancy on subsequent child development. Each of these cohorts evaluated the association between prenatal chlorpyrifos and/or OP exposure (with adverse neurodevelopmental outcomes in children through age 7 years). For the 2014 chlorpyrifos revised human health risk assessment (D424485, D. Drew et al, 12/29/2014), EPA included epidemiologic research results from these three US prospective birth cohort studies but primarily focused on the results of CCCEH since this cohort has published studies on the association between cord blood levels of chlorpyrifos and neurodevelopmental outcomes. The agency retained the FQPA 10X Safety Factor (SF) in the 2014 chlorpyrifos revised risk assessment, in large part, based on the findings of these studies.

In the 2015 updated literature review (OPP/USEPA; D331251; 9/15/15), the agency conducted a systematic review expanding the scope of the 2012/2014 review focused on US cohort studies with particular emphasis on chlorpyrifos. The expanded 2015 review includes consideration of the epidemiological data on any OP pesticide, study designs beyond prospective cohort studies, and non-U.S. based studies. The updated literature review identified seven studies which were relevant (Bouchard et al., 2010; Fortenberry et al., 2014; Furlong et al., 2014; Guodong et al., 2012; Oulhote and Bouchard, 2013; Zhang et al., 2014; Shelton et al., 2014). These seven studies have been evaluated in context with studies from the 2012/2014 review (D424485, D. Drew et al, 12/29/2014). Only a brief summary is provided below.

The OP exposure being assessed in many of these studies used concentrations of urinary dialkyl phosphate metabolites (DAPs) as the urinary biomarker. Total DAPs is a non-specific measure of OP exposure and is the sum of six separate molecules - three dimethyl alkylphosphate

[7] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0170

(DMAP) molecules of DMP, DMTP, DMDTP, and three diethyl alkylphosphate (DEAP) molecules of DEP, DETP, and DEDTP. Each metabolite is a breakdown product from multiple OPs (Table 4.4.1; CDC, 2008)[8]. Specifically, DMP, DMTP, and DMDTP are associated with 18, 13, and 5 OPs, whereas DEP, DETP, and DEDTP are associated with 10, 10, and 4 OPs, respectively. Thus, using urinary DAPs alone as an exposure measure, it is not possible to separate the exposure and associated effects for single, specific OPs.

Table 4.4.1.CDC Table of organophosphate pesticides and their dialkyl phosphate metabolites (2008).

Pesticide	DMP	DMTP	DMDTP	DEP	DETP	DEDTP
Azinphos methyl	X	X	X			
Chlorethoxyphos				X	X	
Chlorpyrifos				X	X	
Chlorpyrifos methyl	X	X				
Coumaphos				X	X	
Dichlorvos (DDVP)	X					
Diazinon				X	X	
Dicrotophos	X					
Dimethoate	X	X	X			
Disulfoton				X	X	X
Ethion				X	X	X
Fenitrothion	X	X				
Fenthion	X	X				
Isazaphos-methyl	X	X				
Malathion	X	X	X			
Methidathion	X	X	X			
Methyl parathion	X	X				
Naled	X					
Oxydemeton-methyl	X	X				
Parathion				X	X	
Phorate				X	X	X
Phosmet	X	X	X			
Pirimiphos-methyl	X	X				
Sulfotepp				X	X	
Temephos	X	X				
Terbufos				X	X	X
Tetrachlorviphos	X					
Trichlorfon	X					

DMP = dimethylphosphate; DEP = diethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate.

For studies which measured urinary 3,5,6-trichloro-2-pyridinol (TCPy) (e.g., Fortenberry et al, 2014; Eskenazi et al, 2007; Whyatt et al, 2009), this metabolite can be derived from chlorpyrifos, chlorpyrifos-methyl, and the herbicide triclopyr. TCPy is also the primary environmental degradate of chlorpyrifos, chlorpyrifos-methyl, and triclopyr; thus exposure can be found

[8] http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l26opd_c_met_organophosphorus_pesticides.pdf

directly on food treated with these pesticides. CCCEH studies have largely used chlorpyrifos measured in cord blood as the specific biomarker (e.g., Lovasi et al, 2010; Whyatt et al, 2004; Rauh et al, 2011). The CHARGE study (Shelton et al, 2015) did not measure biomarkers but instead used geospatial analysis to focus on the residential proximity to OP exposure using data from the California Department of Pesticide Regulation, with five OPs accounting for a total of 73% of the pesticide applied near residential settings (chlorpyrifos, acephate, diazinon, bensulide, and dimethoate).

Similarly, DAPs can be found directly on food following OP applications (Zhang et al, 2008; Chen et al, 2012). Specifically, studies have shown that DAPs may form as environmental degradates from abiotic hydrolysis, photolysis, and plant metabolism (Zhang et al, 2008; Chen et al, 2012; Racke et al, 1994). Furthermore, since these DAPs are excreted more rapidly and extensively than the parent OPs (Zhang et al, 2008; Forsberg et al, 2008), direct exposure to DAPs may lead to an overestimate of OP exposure when using urinary DAPs as a biomarker of OP exposure. The agency recognizes that this is a source of uncertainty when using DAPs for assessing OP exposure and will continue to monitor this issue in future assessments.

With respect to neurological effects near birth, the CHAMACOS and Mt. Sinai cohorts measured neurological effects at birth, and observed a putative association with total DEAP, total DMAP, and total DAP exposure (Engel et al., 2007; Young et al., 2005). Similarly, a Chinese study (Zhang et al., 2014) reported statistically significant associations between for total DEAPs, total DMAPs, and total DAPs from prenatal OP pesticide exposure and neonatal neurodevelopment assessed 3 days after birth. However, another cross-sectional Chinese study, Guodong et al (2012), observed no association with urinary DAPs and a developmental quotient score for 23-25 month old children.

The 3 US cohorts (CCCEH, Mt. Sinai, CHAMACOS) each reported evidence of impaired mental and psychomotor development, albeit not consistent by age at time of testing (ranging from 6 month to 36 months across the three cohorts). Attentional problems and ADHD were reported by three prospective cohorts [Rauh et al, 2006; Eskenazi et al., 2007; Marks et al, 2010; and Fortenberry et al (2014)] investigators with additional support from a case control study, Bouchard et al. (2010). The exposure metric varied among these studies. Specifically, Fortenberry et al (2014) found suggestive evidence of an association with TCPy and ADHD in boys whereas statistically significant associations were observed by Rauh et al (2006) with chlorpyrifos exposure and ADHD. Eskenazi et al (2007) reported associations with total DMAPs and total DAPs and ADHD; Marks et al (2010) reported associations with total DEAP, DMAP, and total DAP exposure and ADHD. In a national cross-sectional study of Canadian children, using 2007-2009 data for children age 6-11 years (Oulhote and Bouchard, 2013), there were no overall statistically significant associations observed between child urinary DEAP, DMAP, or total DAP metabolite levels and parentally reported behavioral problems. In contrast, Bouchard et al. (2010), looking at U.S. children age 8-15 years in the 2000-2004 National Health and Nutrition Examination Survey (NHANES), observed a positive association between attention and behavior problems and total DAPs and DMAPs, but not DEAPs. As part of their analysis, Oulhote and Bouchard (2013) noted that their outcome assessment for behavioral problems may not have been as sensitive as Bouchard et al (2010), which may in part account for the difference in the observed results from these studies.

In addition, the 3 US cohorts and the CHARGE study have reported suggestive or positive associations between OP exposure and autism spectrum disorders (Rauh et al., 2006; Shelton et al., 2014; Eskenazi et al, 2007; Furlong et al., 2014). Specifically, Furlong et al (2014) documented suggestive evidence of an association between total DEAP exposure and reciprocal social responsiveness among blacks and boys. Eskenazi et al (2007) reported a statistically significant association between pervasive developmental disorder (PDD) and total DAP exposure, whereas Eskenazi et al (2010) reported non-significant, but suggestive, increased odds of PDD of 2.0 (0.8 to 5.1; p=0.14). Rauh et al (2006) documented a significant association between PDD and specifically chlorpyrifos exposure. Both PDD and reciprocal social responsiveness are related to the autism spectrum disorder. Using a different exposure assessment method (geospatial analysis and residential proximity to total OP exposure), Shelton et al (2014) also showed statistically significant associations between total OP exposure and ASD. While these studies vary in the magnitude of the overall strength of association, they have consistently observed a positive association between OP exposure and ASD. Finally, CCCEH, Mt. Sinai, CHAMACOS have reported an inverse relation between the respective prenatal measures of chlorpyrifos and intelligence measures at age 7 years (Rauh et al. ,2011; Engel et al., 2011; Bouchard et al., 2011).

Across the epidemiology database of studies, the maternal urine, cord blood, and other (meconium) measures provide evidence that exposure did occur to the fetus during gestation but the actual level of such exposure during the critical window(s) of susceptibility is not known. While significant uncertainties remain about the actual exposure levels experienced by mothers and infant participants in the children's health cohorts, it is unlikely that these exposures resulted in AChE inhibition. As part of the CHAMACOS study, Eskenazi et al. (2004) measured AChE activity and showed that no differences in AChE activity were observed. The biomarker data (chlorpyrifos) from the Columbia University studies are supported by the agency's dose reconstruction analysis using the PBPK-PD model (D424485, D. Drew et al, 12/29/2014). Following the recommendation of the FIFRA SAP (2012), the agency conducted a dose reconstruction analysis of residential uses available prior to 2000 for pregnant women and young children inside the home. The PBPK-PD model results indicate for the highest exposure considered (i.e., indoor broadcast use of a 1% chlorpyrifos formulation) <1% RBC AChE inhibition was produced in pregnant women. While uncertainty exists as to actual OP exposure at (unknown) critical windows of exposure, EPA believes it is unlikely individuals in the epidemiology studies experienced RBC AChE inhibition.

A review of the scientific literature on potential modes of action/adverse outcome pathways (MOA/AOP)[9] leading to effects on the developing brain was conducted for the 2012 FIFRA SAP meeting (USEPA, 2012) and updated for the December 2014 chlorpyrifos revised risk assessment (D424485, D. Drew et al, 12/29/2014). In short, multiple biologically plausible hypotheses and pathways are being pursued by researchers that include targets other than AChE inhibition, including cholinergic and non-cholinergic systems, signaling pathways, proteins, and others. However, no one pathway has sufficient data to be considered more credible than the others. The fact that there are, however, sparse AOP data to support the *in vitro* to *in vivo*

[9] Mode of action (MOA) and adverse outcome pathways (AOPs) describe a set of measureable key events that make up the biological processes leading to an adverse outcome and the causal linkages between such events.

extrapolation, or the extrapolation from biological perturbation to adverse consequence significantly limits their quantitative use in risk assessment. The SAP concurred with the agency in 2008 and 2012 about the lack of definable key events in a MOA/AOP leading to developmental neurobehavioral effects. However, since the 2014 literature review, there are no substantive changes in the ability to define and quantitate steps in an MOA/AOP leading from exposure to effects on the developing brain. Published and submitted guideline DNT laboratory animal studies have been reviewed for OPs as part of the 2012/2014 review (D424485, D. Drew et al, 12/29/2014) and the updated 2015 review (OPP/USEPA; D331251; 9/15/15). Neurobehavioral alterations in laboratory animals were often reported, albeit at AChE inhibiting doses, but there was generally a lack of consistency in terms of pattern, timing, or dose-response for these effects, and a number of studies were of lower quality. However, this information does provide evidence of long-lasting neurodevelopmental disorders in rats and mice following gestational exposure.

At this time, a MOA(s)/AOP(s) has/have not been established for neurodevelopmental outcomes. This growing body of literature does demonstrate, however, that OPs are biologically active on a number of processes that affect the developing brain. Moreover, there is a large body of *in vivo* laboratory studies which show long-term behavioral effects from early life exposure, albeit at doses which cause AChE inhibition. EPA considers the results of the toxicological studies relevant to the human population, as qualitatively supported by the results of epidemiology studies. The agency acknowledges the lack of established MOA/AOP pathway and uncertainties associated lack of ability to make strong causal linkages and unknown window(s) of susceptibility. These uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies reviewed in the 2012/2014 and 2015 literature reviews represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements. Despite all these differences in study design, with the exception of two negative studies in the 2015 literature review (Guodong et al, 2012; Oulhote and Bouchard, 2013), authors have identified associations with neurodevelopmental outcomes associated with OP exposure across four cohorts and twelve study citations. Specifically, there is evidence of delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children who were exposed to OPs during gestation. Investigators reported strong measures of statistical association across several of these evaluations (odds ratios 2-4 fold increased in some instances), and observed evidence of exposures-response trends in some instances, *e.g.*, intelligence measures.

As section 408(b)(2)(C) of the FFDCA instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children." Given the totality of the evidence, there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X FQPA Safety Factor. For the ethoprop DRA, a value of 10X has been applied. Similarly, a

database uncertainty factor of 10X will be retained for occupational risk assessments. The agency will continue to evaluate the epidemiology studies and pursue approaches for quantitative or semi-quantitative comparisons between doses which elicit AChE inhibition and those which are associated with neurodevelopmental outcomes prior to a revised human health risk assessment.

4.5 Safety Factor for Infants and Children (FQPA SF)

As noted above, the lack of an established MOA/AOP makes quantitative use of the epidemiology studies in risk assessment challenging, particularly with respect to determining dose-response, critical duration of exposure, and window(s) of susceptibility. However, exposure levels in the range measured in the epidemiology studies are likely low enough that they are unlikely to result in AChE inhibition. Epidemiology studies consistently identified associations with neurodevelopmental outcomes associated with OP exposure such as delays in mental development in infants (24-36 months), attention problems and autism spectrum disorder in early childhood, and intelligence decrements in school age children. Therefore, there is a need to protect children from exposures that may cause these effects; this need prevents the agency from reducing or removing the statutory FQPA Safety Factor. **Thus, the FQPA 10X Safety Factor will be retained for ethoprop for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.**

4.5.1 Completeness of the Toxicology Database

The database of toxicology studies for ethoprop is complete and adequate for characterizing ethoprop toxicity. The ethoprop toxicity database includes developmental studies in rat and rabbit, a reproductive toxicity study, neurotoxicity studies (acute, subchronic, and developmental) and comparative cholinesterase studies (acute and repeat-dosing in adults and pups).

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

4.5.2 Evidence of Neurotoxicity

Ethoprop is an OP with a neurotoxic AOP; neurotoxicity is the most sensitive effect across all species, routes, and lifestages and is being used in deriving PODs. Neurotoxicity related to inhibition of AChE by ethoprop have been noted in a number of studies including the ACN, SCN, and the DNT studies. Neurotoxicity included numerous clinical signs, and motor abnormalities as discussed above. The points of departures selected for this risk assessment are protective of these effects.

4.5.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Rat and rabbit developmental toxicity studies are available and do not show any susceptibility, although cholinesterase activity was not monitored in those studies. Similarly, the rat reproductive toxicity study does not show any life stage susceptibility. Well-conducted CCA studies (single and repeat dose phases) with time to peak AChE measurements were available, and provided dose-response data from potentially susceptible lifestages; i.e., pregnant dams and post-natal pups. The CCA studies indicated quantitative sensitivity (both acute and repeat dosing) in the pups for brain AChE inhibition compared with adult rats, and also did not reveal any significant differences (as shown by the range of BMD values) between RBC and brain AChE inhibition in the pups.

Comparisons across studies (e.g., DNT vs CCA) are problematic for a number of reasons, but can reveal patterns in a qualitative, but not quantitative, sense. Based on the overall results from BMD modeling, the BMD estimates for pups from the CCA studies are lower than the estimates for the dams from the DNT study, and has been used for acute and steady-state points of departure.

As discussed in Section 4.4, there is uncertainty in the human dose-response relationship for neurodevelopmental effects and this warrants retention of the FQPA Safety Factor for the population subgroups that include infants, children, youths, and women of childbearing age for all exposure scenarios.

4.5.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to the exposure databases. The unrefined acute dietary assessment incorporated tolerance level residues, default processing factors and 100% crop treated. The unrefined steady-state dietary exposure assessments are not expected to underestimate dietary (food and water) exposures.

4.6 Toxicity Endpoint and Point of Departure Selections

4.6.1 Dose-Response Assessment

Tables 4.5.4.1 and 4.5.4.2 summarize the ethoprop toxicity endpoints and PODs selected from an evaluation of the database. This endpoint selection was based on a weight of the evidence evaluation using the following considerations:

- *Relative sensitivity of the brain and RBC compartments*: For ethoprop, **the RBC compartment was consistently more sensitive than the brain compartment as evident from the well-conducted CCA studies (acute and repeat dose phases).** The results of the DNT study provide support for the greater sensitivity of the RBC compartment. As such, OPP has emphasized the RBC AChE data in POD derivation.

Potentially susceptible populations (fetuses, juveniles, pregnancy): The well-conducted CCA studies (acute and repeat dosing in adults and pups) revealed lifestage sensitivity with regard to AChE inhibition. **Overall, pups were found to be more sensitive than adults to RBC cholinesterase inhibition by a factor of >2-fold. The relative sensitivity of pups to**

adults to brain cholinesterase inhibition could not be accurately determined because of lack of dose response in adults. There was no gestational component to the CCA study. It is important to note that the results of the dietary DNT study cannot readily be compared with the CCA study which was performed by the gavage route of exposure, inclusion of time to peak inhibition measurements (different for pups vs. adults), and the lack of lactational exposure of pups to ethoprop. For example, the differences in magnitude between AChE measurements of PND21 pups in the DNT study vs. PND 11 pups in the CCA study can be explained by the following considerations: (1) exposure to ethoprop in the DNT study derives from lactation and 8-days of food consumption, while the CCA study involves 11-days of direct gavage dosing. It takes a longer time to reach an internal concentration with the diet and another possible explanation could be minimal chemical absorption from in utero/lactational exposures. The CCA study with gavage dosing is more protective and matches a bolus dose from exposure via a baby bottle; (2) in the CCA study, AChE measurements were made at peak exposure while the DNT AChE measurements were most likely the day after treatment; and (3) pups recover faster than adults due to their increased protein synthesis. However, both studies do show patterns in a qualitative, rather than quantitative sense. In this regard, the CCA studies indicated that PND11 pups were more sensitive than adults (including nonpregnant females) with respect to AChE inhibition.

- *Route of exposure:* It is preferred to match, to the degree possible, the route of exposure in the toxicity study with that of the exposure scenario(s) of interest. In the case of ethoprop, there are oral, dermal, and inhalation studies which contain quality dose response AChE data.

- *Duration of exposure:* It is preferred to match, to the degree possible, the duration of toxicity study with that of the exposure duration of interest. In the case of ethoprop, there are single-day and steady-state oral studies. For the dermal and inhalation toxicity studies, there were no single-day AChE measurements; however, there were measurements at steady-state.

- *Consistency across studies:* In cases where multiple datasets are available for a single duration, it is important to evaluate the extent to which data are consistent (or not) across studies. The ethoprop database has striking consistency across studies which allows for PODs to be derived from multiple critical studies thereby increasing the confidence in such values.

Acute Dietary (all populations)

As shown in Appendix Table A.2.1, results from single dosing exposures with ethoprop provide only one dataset appropriate for this exposure scenario (RBC and brain AChE data in pups for postnatal day 11 (PND11), in addition to adult male and female rats.

A PoD for the acute dietary (all populations) exposure scenario was derived from the results of a high quality, well-conducted acute CCA rat study (MRID 4627801). A $BMDL_{10}$ of ≈ 0.42 mg/kg/day associated with RBC AChE inhibition in female pups (PND11) was selected as a

suitable PoD for the acute dietary (all populations) exposure scenario. The corresponding BMD_{10} was ≈ 0.55 mg/kg/day.

RBC AChE inhibition in pups was selected for the POD because $BMDL_{10}$′s for this compartment were slightly lower than that estimated from the pup brain AChE data. In addition, the brain AChE data (in contrast to RBC AChE) for the adult rats did not provide reliable fits from benchmark dose analyses because of a lack of a dose-response relationship. For the adults, the RBC compartment is more sensitive than the brain compartment. The $BMDL_{10}$ based on RBC AChE inhibition in PND11 females is protective of effects observed in adult rats in the ACN, SCN and DNT studies, the male PND11 (CCA studies) and the PND21 pups in the DNT study. Data from the PND11 pups represent highly exposed sub-populations (infants and young children) and are appropriate for the POD derivation.

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation and, 10x for FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4)) is applied to the $BMDL_{10}$ to obtain an acute population adjusted dose (aPAD) of 0.00042 mg/kg/day. The only population subgroup that the FQPA safety factor is not retained is adults 50-99; therefore, the aPAD for this population subgroup is 0.0042 mg/kg/day.

Steady-State Dietary (all populations)

A POD for the steady-state dietary (all populations) exposure scenario was derived from the results of high quality, well-conducted CCA (repeat dosing) rat study (MRID 46636401). A $BMDL_{10}$ of ≈ 0.07 mg/kg/day associated with RBC AChE inhibition in PND11 male pups was selected as a suitable PoD for the steady-state dietary (all populations) exposure scenario. The corresponding BMD_{10} was ≈ 0.11 mg/kg/day.

This endpoint is considered appropriate for steady-state dietary exposure due to the oral route of administration and the duration of exposure. The study and endpoints were selected because they are protective of effects observed in all of the other available studies for all lifestages. The PND11 pup was selected because this age group and lifestage is more sensitive than adults to ethoprop-induced RBC and brain AChE inhibition following repeated exposure.

The POD of 0.07 mg/kg/day for RBC AChE inhibition is supported by several other studies including:

- $BMDL_{10}$ of 0.11 mg/kg/day for RBC AChE inhibition in PND11 female pups in the CCA (repeat dosing) rat study (MRID 46636401).
- $BMDL_{10}$′s of 0.12 and 0.16 mg/kg/day for brain AChE inhibition in PND11 male and female pups, respectively, in the CCA (repeat dosing) rat study (MRID 46636401).
- $BMDL_{10}$ of 0.13 mg/kg/day for RBC AChE in dams dosed from GD 6-20 in the range-finding DNT study (MRID 46364802).

An uncertainty factor of 1000X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 10X for FQPA SF due to uncertainty in the human dose-response

relationship for neurodevelopmental effects (See section 4.4)) is applied to the $BMDL_{10}$ to obtain an population adjusted dose (ssPAD) of 0.000065 mg/kg/day. The only population subgroup that the FQPA SF is not retained is adults 50-99; therefore, the ssPAD for this population subgroup is 0.00065 mg/kg/day.

Incidental Oral, Short-Term

Same as Steady State Dietary Endpoint. A total uncertainty factor of 1,000X (level of concern, LOC=1,000) is appropriate for non-occupational incidental oral exposure (i.e., 10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X FQPA SF due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4)).

Dermal, Steady State

Two dermal toxicity studies on liquid (70% a.i.) ethoprop, one in rabbits and the other in rats, were available. There was a study (MRID 45034801) on the granular formulation (19.34% a.i.) that was also available. Since the occupational handler assessment may involve exposures to either the granular or the liquid formulations, depending on the pest and/or crop treated, two separate steady-state dermal PODs were selected for the different formulations. For the liquid formulation, a steady-state dermal POD was selected from a 3-week dermal toxicity study (MRID 41304404) on technical ethoprop in rabbits based on RBC AChE inhibition ($BMDL_{10} \approx$ 0.16 mg/kg/day; $BMD_{10} \approx$ 0.20 mg/kg/day) in the adult female rabbit. This selection was supported by comparable $BMDL_{10}$′s (0.2 – 0.3 mg/kg/day) obtained from the analyses of the RBC AChE data from a 3-week dermal toxicity study (MRID 45074602) in the rat. The RBC compartment, which provided BMD estimates comparable to the brain, was selected to be consistent with other routes (i.e., oral and inhalation) in which RBC was the chosen compartment. The $BMDL_{10}$ of 0.16 mg/kg/day from the dermal rabbit toxicity study is lower than the acute dermal LD_{50} of 7.9 mg/kg in the male rabbit for the liquid formulation.

For the granular formulation, a steady-state dermal POD was selected from the 4-week dermal toxicity study of this formulation in the rat. The lowest $BMDL_{10}$ was 10.4 mg/kg/day based on RBC AChE inhibition in the female rat. Comparable BMD estimates were obtained for this compartment in the male rat. BMD estimates were based on doses corrected for percent active ingredient. No adequate BMD fits were obtained with the brain AChE data. The $BMDL_{10}$ of 10.4 mg/kg/day from the dermal study in the rat is lower than the acute dermal LD_{50} of 31.36 mg/kg in the rabbit for a similar formulation (an acute dermal LD_{50} study in the rat was not available for the granular formulation). Although an acute dermal LD_{50} study in the rat was not available for the granular formulation, the rabbit is more sensitive than the rat with regard to acute toxicity based on data on the technical form of ethoprop. This study is appropriate for the route and duration of exposure.

A total uncertainty factor of 1000X is appropriate for dermal exposures (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X FQPA SF for residential assessments or a database uncertainty factor in occupational assessments due to uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4)).

Inhalation, Steady State

A steady state inhalation POD was selected from a 3-week inhalation toxicity study (MRID 48779601) in rats, based on RBC AChE inhibition ($BMDL_{10} \approx 0.82$ µg/L/day; $BMD_{10} \approx 1.3$ µg/day/L) in the adult male rat. The particle size distribution from this study suggests that most particles were well below the respirable range for an aerosol, suggesting that the exposure was mainly via a gas. Human equivalent concentrations (HECs) and Human Equivalent Doses were calculated from the $BMDL_{10}$ value for various scenarios (See Table 4.5.1) for extrarespiratory effects of a gas. For steady state inhalation exposures, a total uncertainty factor of 300X was applied [3X for interspecies extrapolation, 10X for intraspecies variation, and 10X database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4)).

Table 4.6.1. Ethoprop inhalation BMDL10 values adjusted for toxicity duration and specific breathing rates for various exposure scenarios

Population	Scenario	Toxicity Duration Adjustment		$BMDL_{10}$ (mg/L or mg/m^3)	$BMDL_{10}$ (mg/kg/day; breathing rate specific)		
		hr/day	day/wk		8.3 L/min	16.7 L/min	29 L/min
Occupational	Handler	8	5	0.000825 mg/L	0.035 mg/kg/day	0.071 mg/kg/day	0.123 mg/kg/day
Residential	Bystander	24	7	0.147 mg/m^3	NA	NA	NA

Biomonitoring, Multi-route exposure, Steady State

Occupational handler biomonitoring data are available for use in the ethoprop occupational handler assessment, where a urinary metabolite (O-ethyl-S-propylphosphorothioate) was converted to ethoprop equivalents. Because the biomonitoring data allows for total ethoprop exposure without distinguishing between exposure routes (i.e., dermal vs. inhalation), a $BMDL_{10}$ of ≈ 0.065 mg/kg/day associated with RBC AChE inhibition in PND11 pups was selected as a suitable PoD for the biomonitoring exposure scenario. The corresponding BMD_{10} was ≈ 0.11 mg/kg/day.

A total uncertainty factor of 1000X (level of concern, LOC=1,000) is appropriate for the biomonitoring risk estimation [i.e., 10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X database uncertainty factor incorporating uncertainty in the human dose-response relationship for neurodevelopmental effects (See section 4.4)].

4.6.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined if they have the same toxicological effects. PODs for the incidental oral, dermal, and inhalation routes are all derived from RBC

AChE inhibition. As a result, it is appropriate to combine dermal and inhalation exposures in the occupational handler assessment (See Section 9.1.1 for additional information).

4.6.3 Cancer Classification and Risk Assessment Recommendation

Ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. A quantitative cancer risk assessment is required; The Q_1* for ethoprop is $2.81x10^{-2}$ mg/kg/day^{-1}.

4.6.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 identifies the PODs and UF used in non-occupational (dietary, volatilization, and spray drift assessments).
Table 4.5.4.2 identifies the PODs and UFs used in the occupational handler risk assessment.

Table 4.6.4.1 Summary of Toxicological Doses and Endpoints for Ethoprop for Use in Non-occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty / FQPA Safety Factors[a]	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations including females 13-49 years of age)	$BMDL_{10}$ = 0.4187 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x	Acute PAD = 0.00042 mg/kg/day	Acute CCA Study (MRID 4627801) in the rat – PND11. BMD_{10} = 0.5498 mg/kg/day Inhibition of RBC AChE in PND11 pups.
Acute Dietary (Adults 50-99)	$BMDL_{10}$ = 0.4187 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute PAD = 0.0042 mg/kg/day	Acute CCA Study (MRID 4627801) in the rat – PND11. BMD_{10} = 0.5498 mg/kg/day Inhibition of RBC AChE in PND11 pups.
Steady-State Dietary (all populations	$BMDL_{10}$ = 0.0653 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x	Steady State PAD = 0.000065 mg/kg/day	Repeat CCA Study (MRID 46636401) in the rat – PND11. BMD_{10} = 0.1056 mg/kg/day Inhibition of RBC AChE in PND11 pups
Steady-State Dietary (Adults 50-99)	$BMDL_{10}$ = 0.0653 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Steady State PAD = 0.00065 mg/kg/day	Repeat CCA Study (MRID 46636401) in the rat – PND11. BMD_{10} = 0.1056 mg/kg/day Inhibition of RBC AChE in PND11 pups

Table 4.6.4.1 Summary of Toxicological Doses and Endpoints for Ethoprop for Use in Non-occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty / FQPA Safety Factors[a]	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Steady-State (3 weeks & longer)	$BMDL_{10}$ = 0.0653 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 10x	Residential LOC = 1,000	Repeat CCA Study (MRID 46636401) in the rat – PND11. BMD_{10} = 0.1056 mg/kg/day Inhibition of RBC AChE in PND11 pups
Dermal Steady-State (3 weeks & longer) Technical - Liquid formulation[a]	$BMDL_{10}$ = 0.1625 mg/kg/day	UF_A=10x UF_H=10x FQPA SF= 10x	Residential LOC = 1,000	3-week dermal toxicity study (MRID 41304404) in rabbits BMD_{10} = 0.2035 mg/kg/day Inhibition of RBC AChE in adult female rabbits.
Inhalation Steady-State (3 weeks & longer)	$BMDL_{10}$ = 0.8245 µg/L/day[b]	UF_A=3x UF_H=10x FQPA SF= 10x	Residential LOC = 300	4-week inhalation toxicity study (MRID 48779601) BMD_{10} = 1.296 µg/L/day Inhibition of RBC AChE in adult male rat.
Cancer (oral, dermal, inhalation)	Classification: "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. The Q_1* for ethoprop is 2.81×10^{-2} $mg/kg/day^{-1}$.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). aPAD = acute population adjusted dose. ssPAD = Steady state population adjusted dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[a] While there is a separate endpoint and POD selected for the ethoprop granular formulation, it is applicable only to the occupational assessment. The steady-state dermal endpoint and POD is identified here for the spray drift assessment.

[b] See Appendix A; Table A3 for adjusted inhalation $BMDL_{10}$ values for toxicity duration and specific breathing rates for various exposure scenarios**.**

[a] FQPA SF retained for infants, children, youths, and women of childbearing age for all exposure scenarios due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). This includes all exposure scenarios, except the dietary exposure scenarios for the population subgroup adults 50-99 for which the FQPA SF has been reduced to 1X.

Table 4.6.4.2 Summary of Toxicological Doses and Endpoints for Ethoprop for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal – Steady-State (3 weeks & longer) Technical - Liquid formulation	$BMDL_{10}$ = 0.1625 mg/kg/day	UF_A=10x UF_H=10x UF_{DB}=10x[b]	Occupational LOC for MOE = 1,000	3-week dermal toxicity study (MRID 41304404) in rabbits BMD_{10} = 0.2035 mg/kg/day Inhibition of RBC AChE in adult female rabbits.
Dermal – Steady-State (3 weeks & longer) Granular formulation (19.3% a.i.)	$BMDL_{10}$ = 10.4 mg/kg/day	UF_A=10x UF_H=10x UF_{DB} = 10x[b]	Occupational LOC for MOE = 1,000	4-week dermal toxicity study (MRID 45034801) in rats BMD_{10} = 15.7 mg/kg/day (BMD modeling based on doses adjusted for a.i.) Inhibition of RBC AChE in adult female rat.
Inhalation Steady-State (3 weeks & longer)	$BMDL_{10}$ = 0.8245 µg/L/day[a]	UF_A=3x UF_H=10x UF_{DB} = 10x[b]	Occupational LOC for MOE = 300	4-week inhalation toxicity study (MRID 48779601) BMD_{10} = 1.296 µg/L/day Inhibition of RBC AChE in adult male rat.
Biomonitoring Exposure Assessment – Multi-route Steady-State (3 weeks & longer)	$BMDL_{10}$ = 0.0653 mg/kg/day	UF_A= 10x UF_H=10x UF_{DB} = 10x	Occupational LOC = 1,000	Repeat Oral CCA Study (MRID 46636401) in the rat – PND11. BMD_{10} = 0.1056 mg/kg/day
Cancer (oral, dermal, inhalation)	Ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. The Q_1* for ethoprop is $2.81x10^{-2}$ mg/kg/day^{-1}.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[a] See Appendix A; Table A3 for adjusted inhalation $BMDL_{10}$ values for toxicity duration and specific breathing rates for various exposure scenarios**.**

[b] UF_{DB} for occupational dermal and inhalation exposures = database uncertainty factor for uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

4.7 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for ethoprop, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), ethoprop is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[10] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

Ethoprop is on List 1 for which EPA has received all of the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2008-0560 for ethoprop). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and Tier 1 screening battery, please visit our website[11].

[10] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[11] Available: http://www.epa.gov/endo/

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The metabolism of ethoprop in plants and livestock was extensively discussed in the residue chemistry chapter of the ethoprop RED (DP# D239294, J. Abbotts, 3/27/1998). The degradation of ethoprop in the environment is discussed in a memo by M. Barrett (DP Barcodes D428028, 09-15-2015).

The residues of concern for the acute and steady state risk assessments in crops are parent and Metabolites II and III (S-ME and O-ME); for cancer dietary risk, the residues of concern are parent and Metabolites II through IV (S-ME, O-ME and M-1). For water, the only residue of concern is parent, ethoprop. Metabolites II and III are AChE inhibitors, but Metabolite IV is not. The environmental degradate SSDP is also of concern for cancer risk assessment. These metabolites are also rat metabolites. Structures of the parent and metabolites may be found in Table 2.2.

Since field trial data on the metabolites are not available, metabolite ratios were estimated from metabolism and rotational crop studies. Further information on the development of the ratios may be found in the anticipated residue memo (C. Olinger, DP Barcodes 352476 and 352477, 07/03/2008).

5.1.2 Summary of Environmental Degradation

Ethoprop degrades primarily by microbial metabolism as well as the abiotic process of hydrolysis. The aerobic soil metabolism half-life is 100 days in the guideline study. Field dissipation half-lives are 3 to 60 days at approximately 24 different sites. There are no acceptable anaerobic aquatic metabolism studies available but a 100 day half-life was observed in an anaerobic soil metabolism study. Degradation due to hydrolysis varies with pH, with estimated half-lives at 25 °C of 205 days for acidic (pH 5) waters, 150-155 days for waters with neutral pH (pH 7), and 39 days for alkaline waters (pH 9). Ethoprop is not subject to photolysis. Ethoprop is classified as highly mobile with a median K_{oc} of 109 in five test soils[1].

No degradate of ethoprop in soil and water laboratory studies was observed at >10% of the applied parent at any time during the studies. O-ethyl-S-propyl phosphorodithioate (also known as metabolite M-1) is a common metabolite found in soil and water and is a hydrolysis product; subsequent to the formation of M-1 further degradation and mineralization is observed. For the purposes of drinking water exposure evaluation for the human health risk assessment parent ethoprop is the only residue of concern.

[1] McCall, P. J., Swann, R. L., Laskowski, D. A., Unger, S. M., Vrona, S. A. and Dishburger, H. J. 1980. Estimation of chemical mobility in soil from liquid chromatographic retention times, Bull. Environ. Contam. Toxicol., 24, 190–195.

5.1.3 Comparison of Metabolic Pathways

For reregistration and risk assessment purposes, adequate plant and livestock metabolism data are available. The metabolism of ethoprop in plants and livestock was extensively discussed in the residue chemistry chapter of the ethoprop RED (DP# D239294, J. Abbotts, 3/27/1998).

For plants, ethoprop is metabolized primarily to parent and metabolites II and III and water is metabolized into parent; for cancer dietary risk, the residues of concern are parent and metabolites II, III, and IV. See Table 3.1 for additional information on the metabolites.

For livestock, ethoprop is metabolized primarily to metabolites III and/or IV which together accounted for $\leq$2% of the total radioactive residues in liver of hens and goats (J. Abbotts, D239294, 03/27/1998).

For drinking water, ethoprop is the only residue of concern that exceeds 10% in the environment.

Metabolites III and IV are both found in rat metabolism studies however it is likely that Metabolite II also forms.

5.1.4 Residues of Concern Summary and Rationale

The Health Effects Division (HED) Metabolism Committee found that for plants, acute and steady state non-cancer dietary risk, the residues of concern in crops were parent and metabolites II and III. For plants, cancer dietary risk residues of concern are parent and metabolites II, III, and IV. Table 5.1.4.1 summarizes the metabolites and degradates to be included in the human health risk assessment and in the tolerance expression. Drinking water residues of concern were parent only, ethoprop for both tolerance and risk assessment.

Table 5.1.4.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment Non-Cancer (Cancer)	Residues included in Tolerance Expression
Plants	Primary Crop	Metabolites II and III (II, III & IV)	Ethoprop
	Rotational Crop	Metabolites II and III (II, III & IV)	Ethoprop
Livestock	Ruminant	Metabolites II and III (II, III & IV)	Ethoprop
	Poultry	Metabolites II and III (II, III & IV)	Ethoprop
Drinking Water		Ethoprop	Ethoprop

5.2 Food Residue Profile

HED has previously evaluated residue data depicting the magnitude of ethoprop residues of concern in banana; bean, lima; snap, succulent; cabbage; field corn (forage, stover, and grain); sweet corn (forage, stover, and kernel plus cob with husk removed); cucumber; hop, dried cones,

peppermint tops; pineapple; spearmint tops; sugarcane, cane; and sweet potato roots[12]. The Nature of the Residue (NOR) in plants is adequately understood based on cabbage, corn, and potato metabolism studies. The HED Metabolism Committee (K. Farwell, 02/06/1998) found that for acute and chronic non-cancer dietary risk, the residues of concern in crops were parent and metabolites II and III; for cancer dietary risk, residues of concern are parent and metabolites II, III, and IV. The NOR in livestock is adequate based on ruminant and poultry metabolism studies. The Agency (R. Perfetti, 06/22/1994) concluded that the data from the metabolism studies indicate that a Category 3 situation [40 CFR 180.6 (a) (3)] exists for livestock commodities. Ethoprop was not detected in milk, eggs, or tissues from goats and hens dosed orally for seven consecutive days with ethoprop at levels equivalent to 32 ppm and 2.09 ppm, respectively in the diet.

An adequate confined rotational crop study is available and indicates that residues of ethoprop in rotational crops are qualitatively similar to the residues resulting from the direct application of ethoprop to the primary crops. Ethoprop residues of concern were detected at >0.01 ppm in/on spinach from the 31-day plant-back interval, radish roots and wheat straw from 31- and 123-day PBIs, and wheat forage from 31-, 123, and 365-day PBIs. Based upon results of the confined rotational crop study, limited field accumulation studies in rotational crops were required (D239294, J. Abbots, 03/27/1998). Adequate data are available from limited rotational crop field trials complete this deficiency (D394590, C. Olinger, 12/10/2008).

5.3 Water Residue Profile

Drinking Water Exposure Assessment; M. Barrett; 09-15-2015; D428028

The drinking water residues used in the dietary risk assessment were provided by EFED and incorporated directly into this dietary assessment.

There were no degradates of ethoprop in soil and water laboratory studies that exceeded 10% of the applied parent at any time during the studies. For the purposes of drinking water exposure evaluation, the parent ethoprop is the only residue of concern.
EFED provided groundwater (Pesticide Root Zone Model for Groundwater (PRZM-GW), version 1.0, August 31, 2012) EDWCs. EFED stated that the groundwater EDWC was appropriate to use in the acute dietary exposure assessment. For the steady-state dietary exposure assessment, EFED provided daily time-series outputs that simulate 29 years of residues of ethoprop in drinking water. These distributions were adjusted so that the data points were 21-day rolling averages. These values were incorporated into RDFs for use in DEEM.

5.4 Dietary Risk Assessment

Ethoprop acute, steady-state, and cancer dietary risk assessments were conducted using DEEM-FCID, Version 3.16, which incorporates consumption data from USDA's NHANES/WWEIA. This dietary survey was conducted from 2003 to 2008. The analyses were performed to support the Registration Review of ethoprop.

[12] Available: CFR §180.262

Because the estimated drinking water concentration from EFED exceeded HED's level of concern, a Drinking Water Level of Comparison (DWLOC) was calculated for acute, steady state, and cancer assessments assuming that the DWLOC was equal to 0% and 100% of the available risk cup. The body weight and water consumption of the subpopulation that was expected to be exposed with the highest level of ethoprop residue was incorporated in a DWLOC calculation. Each respective population adjusted dose for acute (aPAD), steady state (ssPAD), and cancer (Q_1*) was used to represent the available risk cup.

5.4.1 Description of Residue Data Used in Dietary Assessment

The dietary assessments completed for ethoprop used tolerance level residue values. Applicable default processing factors for commodities for which processing studies are required and are not available, were used in this assessment. All tolerance values for registered crops were at 0.02 ppm and can be found in the 40 Code of Federal Regulations (CFR) §180.262. Tolerances are not required for residues in livestock commodities since there is no reasonable expectation of detectable residues, 40 CFR §180.6(a)3. Because general tolerances are established for ethoprop (*O*-ethyl-*S*,*S*-dipropylphosphorodithioate) and not the metabolites, metabolite ratios were applied to the tolerances before residue values were included in the dietary assessment modeling program.

Table 5.4.1.1 Summary of Metabolite Ratios used for each Dietary Run

Dietary Run Type	Metabolite Ratio (ppm)*
Acute	4.9
Steady State	2.4
Cancer	3.3

*Metabolite Ratios are averages, "Ethoprop Dietary Memo. C. Olinger; D352232

Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources". The most conservative exposure model was used to assess the contributions from drinking water and the Estimated Drinking Water Concentrations (EDWCs) used PRZM-GW.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The unrefined assessment included 100% crop treated for all crops in the acute, steady state, and cancer dietary analyses.

5.4.3 Acute Dietary Risk Assessment

Dietary Assessment; K. King; 08-04-2015; D428313

The acute assessment is unrefined; tolerance level residues, DEEM (ver. 7.81) default processing factors, and 100% crop treated data were utilized.

The acute dietary (food only + drinking water only) exposure analysis is >100 % aPAD at the 95th percentile of exposure for the general population and all population subgroups, except adults 50-99 years of age (Table 5.4.3.1).

The DEEM-FCID analysis of food only for the general US population and the population subgroup with the highest % aPAD value (All Infants), are 260% and 630% reported at the 95th percentile, respectively. The majority of subpopulations exceeded the Health Effects Division's (HED) level of concern and the commodities with the highest percent of total exposure are banana and banana-babyfood.

The DEEM-FCID analysis of water only for the general US population and the population subgroup with the highest % aPAD value (All Infants), are 3,200% and >10,000% reported at the 95th percentile, respectively. All subpopulations exceeded the HED level of concern.

Table 5.4.3.1. Results of Food Only & Water Only Exposure and Risk Analyses

Population Subgroup	Acute (Food Only) 95th Percentile		Acute (Water Only) 95th Percentile	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.001098	260	0.013499	3,200
All Infants (<1 year old)*	**0.002655**	**630**	**0.042824**	**>10,000**
Children 1-2 years old	0.002525	600	0.020770	5,000
Children 3-5 years old	0.002078	500	0.016902	4,000
Children 6-12 years old	0.001447	350	0.012484	3,000
Youth 13-19 years old	0.000947	230	0.010940	2,600
Adults 20-49 years old	0.000799	190	0.013406	3,200
Adults 50-99 years old	0.000634	15	0.012182	2,900
Females 13-49 years old	0.000763	180	0.013641	3,300

*The subpopulation(s) with the highest risk estimates.

5.4.4 Steady-State Dietary Risk Assessment

Dietary Assessment; K. King; 08-04-2015; D428313

The DEEM acute module was used to conduct steady-state assessments using the steady-state endpoint, two-day average dietary exposure, and 21-day rolling water averages. The steady-state assessments are unrefined using tolerance level residues, 100% crop treated, and default processing factors. Food residues cannot confidently be refined because all tolerances are all non-detectable residues which cannot be confidently used for assessment. EFED provided daily time-series outputs that simulate 29 years of residues of ethoprop in water for one scenario (Delmarva sweet corn). These distributions were converted into 21-day rolling averages and incorporated into Residue Distribution Files (RDFs) that were used in DEEM for water, direct all sources and water, indirect all sources.

For the steady state assessment, the *food alone* and *water alone* exposure estimates exceed HED's level of concern for the U.S. population and all population subgroups except adults 50-99 for food only. The results of the steady-state dietary exposure and risk analysis are reported in the Table 5.4.4.1 for food only and water only. The DEEM-FCID analysis results of *food alone* for the general US population and the population subgroup with the highest % ssPAD value (All Infants), are 780% and 1,800%, respectively, reported at the 95th percentile. The DEEM-FCID analysis results of *water alone* for the general US population and the population subgroup with

the highest % ssPAD value (All Infants), are 3,000% and >10,000% reported at the 95th percentile respectively.

Table 5.4.4.1. Results of Food Only & Water Only Exposure and Risk Analyses				
Population Subgroup	**Steady State (Food Only) 95th Percentile**		**Steady State (Water Only) 95th Percentile**	
	Exposure (mg/kg/day)	**% ssPAD**	**Exposure (mg/kg/day)**	**% ssPAD**
General U.S. Population	0.000510	780	0.012684	3,000
All Infants (<1 year old)*	**0.001190**	**1,800**	**0.040883**	**>10,000**
Children 1-2 years old	0.001143	1,800	0.019195	>10,000
Children 3-5 years old	0.000907	1,400	0.015321	>10,000
Children 6-12 years old	0.000653	1,000	0.011423	>10,000
Youth 13-19 years old	0.000406	630	0.010287	>10,000
Adults 20-49 years old	0.000349	540	0.012543	>10,000
Adults 50-99 years old	0.000274	42	0.011665	1,800
Females 13-49 years old	0.000335	520	0.012884	>10,000

*The subpopulation(s) with the highest risk estimates.

5.4.5 Cancer Dietary Risk Assessment

In accordance with the Agency's Cancer Risk Assessment Guidelines (March, 2005), ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. Applying the Q_1* of 0.0281 $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of 7×10^{-6} for *food only*. For *water only*, the exposure value results in a cancer risk estimate of 5×10^{-5}.

Table 5.4.5.1. Results of Food & Water Cancer Risk				
Population Subgroup	**Cancer (Food Only)**		**Cancer (Water Only)**	
	Exposure (mg/kg/day)	**Cancer Risk Estimate**	**Exposure (mg/kg/day)**	**Cancer Risk Estimate**
General U.S. Population	0.000261	7×10^{-6}	0.001746	5×10^{-5}
All Infants (<1 year old)	N/A	N/A	N/A	N/A
Children 1-2 years old				
Children 3-5 years old				
Children 6-12 years old				
Youth 13-19 years old				
Adults 20-49 years old				
Adults 50-99 years old				
Females 13-49 years old				

5.4.6 Characterization of Uncertainties in the Dietary Risk Assessment

Assessment of dietary risk for food is conservative utilizing tolerance level residues (based on method detection limits), 100% crop treated, and default processing factors. However, because most residue levels found in foods were less than the analytical method detection limit, useful refinement of the risk estimates is not possible. The food only risk estimates therefore reflect a worst case estimate of risks; the degree to which actual risks are lower than these estimates cannot be determined in the absence of residue data utilizing more sensitive analytical methods.

Metabolite ratios were multiplied by tolerances to determine residues that incorporated parent and metabolites. Ratios for acute (4.9x), steady state (2.4x), and cancer (3.3) were averaged from C. Olinger's memo (D382076 & D299884, C. Olinger, 07/03/2008).

Drinking water risk estimates are also highly conservative since conservative modeled residues were assumed. Based on the Delmarva sweet corn drinking water scenario, HED's level of concern was exceeded. Therefore, HED calculated a drinking water level of comparison (DWLOC) to help characterize the dietary risk estimates. The DWLOC calculation is a function of the PAD and daily water consumption used to provide the EDWC at the targeted level of concern for dietary assessment (100% of the PAD). Typically, the DWLOC would indicate the residue level allowable in drinking water considering contributions to the total risk cup (i.e., 100% PAD) from food and residential exposures. However, since there are no contributions to the risk cup from residential sources, and since food exposures already fill the total risk cup (i.e., exceed 100% of the PAD), HED has calculated a DWLOC assuming the entire risk cup is available for drinking water. This was done to provide some characterization of risk estimates derived from drinking water.

Because the population subgroup All Infants <1 year old has the highest exposures to residues in drinking water, mitigating the acute, steady-state, and cancer risks for this population subgroup would be protective of all others. Table 5.4.6.1 summarizes the DWLOC calculations for the acute, steady state, and cancer assessments.

Table 5.4.6.1. Summary of DWLOC for Acute, Steady State, and Cancer Assessments

Population	Acute DWLOC (ppb)[1]	Steady State DWLOC (ppb)[1]	Cancer DWLOC (ppb)[2]
US General Population	N/A		4.68
All Infants <1 years old	2.93	0.453	N/A

[1] DWLOC= (% aPAD or % ssPAD mg/kg/day)* (Subpopulation Bodyweight kg)* (1000)/ (DW Consumption L/day)
[2] Cancer DWLOC= (Allowed Exposure)* (Bodyweight kg)* (1000)/ (DW Consumption L/day)

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are currently no registered or proposed residential uses for ethoprop; therefore, a quantitative residential handler and post-application assessment was not performed. Section 6.1/6.2 addresses the potential for non-occupational bystander post-application inhalation exposure (from nearby treated fields). Section 6.3 addresses non-occupational exposure potential from spray drift.

6.1 Non-Occupational Bystander Post-Application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The

agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[13].

The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for ethoprop utilizing the currently available inhalation toxicity and air monitoring data. There is an available air monitoring study with two components relevant to the residential bystander assessment. These components include:

- Application site monitoring conducted in Siskiyou County, CA by the California Air Resource Board (CARB), and
- Ambient air monitoring also conducted in Siskiyou County, CA by the California Air Resource Board (CARB).

Details of the CARB study are provided in the ORE disciplinary memo[14]. Inhalation risk estimates are presented below using both air concentrations measured during application site monitoring and during ambient air monitoring. Application site air monitoring (i.e., also known as field volatility) refers to the collection of air samples around the edges of a treated field during and after a pesticide application. Samples are generally collected for short intervals (e.g., < 8 hours), for at least the first day or two after application with subsequent samples increasing in duration. In this type of study, it is typically known when an application occurred, the equipment used for the application, and the application rate. Application site monitoring data represents an exposure to vapors at or near the field edge resulting from an application.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal pesticide use patterns. Typically, samples are generally taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

Table 6.1.1 provides ethoprop inhalation risk estimates resulting from volatilization for each site. The ethoprop bystander volatilization inhalation exposure assessment compares the maximum and average air concentrations detected in each of the monitoring studies to the steady state HEC for residential bystanders, as no acute HEC is available for ethoprop. This comparison of the

[13] Available: http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219
[14] M. Lloyd; 09-15-2015; D421954

steady state HEC and the available application site monitoring data is a conservative representation of a potential resident who lives next to a treated field and may be exposed to the peak or average concentration of ethoprop volatilizing off the field over a 24-hour period. In addition, both the single peak air concentration per site and the arithmetic mean ethoprop air concentration from the ambient air monitoring study was compared to the steady-state HEC for residential bystanders. Again, because no acute HEC value is available, the comparison of the peak ambient concentrations against the steady state endpoint is a conservative representation of a potential resident of an agricultural area where ethoprop is being applied in multiple field locations.

Even with the conservative use of the steady state endpoint to evaluate peak exposures from the application site and ambient monitoring, none of the application site monitoring locations results in single day risks of concern. None of the air concentrations from either the ambient or application site data available resulted in risk estimates of concern for the steady state analysis.

Table 6.1.1. Residential Bystander: Preliminary Volatilization Risk Analysis.									
Study	**Year of Study**	**Sampler/Site Location**	**Number of samples[c]**	**Duration of samples**	**Duration of sampling period**	**Maximum Air Concentration (mg/m^3)**	**Arithmetic Mean Air Concentration (mg/m^3)**	**Single-Day MOEs[a] (LOC = 300)**	**Steady-state MOEs[b] (LOC = 300)**
Ambient Air Monitoring[d]									
Siskiyou County, CA (CARB)	1998	MacDoel School – MacDoel, CA	28 (3 above the MDL)	24-hour	1 month	2.0E-06	5.0E-07	74,000	290,000
		Doris School – Doris, CA	29 (1 above the MDL)			3.0E-06	3.5E-07	49,000	410,000
		Tule Lake School Bus Barn – Tule Lake, CA	29 (none above MDL)			1.3E-06	6.1E-07	110,000	240,000
		Newell School – Tule Lake, CA	29 (none above MDL)			1.3E-06	3.4E-07	110,000	440,000
Application Site Monitoring[d]									
Siskiyou County, CA (CARB)[e]	1998	East	Each site included 8 samples (including background sample)	Ranged from 3.4-hour to 24-hour samples; taken pre-application & at post-application	3 days	1.3E-04	8.1E-05	1,800	1,100
		East (co-located sampler)				1.4E-04	8.6E-05	1,700	1,100
		North				5.4E-05	2.4E-05	2,700	6,100
		South				2.1E-04	1.2E-04	700	1,400
		West				6.8E-05	2.1E-05	2,200	7,200

a. Single Day MOE = Steady-state HEC (0.147 mg/m^3) / Study maximum air concentration (ng/m^3). LOC = 1000.

b. Steady-state MOE = Steady-state HEC (0.147 mg/m^3) / Study arithmetic mean air concentration (mg/m^3). LOC = 1000.

c. All non-detects and trace concentrations reported. For non-detects, assumed 1/2 Method Detection Limit (MDL) of 0.947 ng/sample – 1.33 ng/m^3. For trace concentrations, assumed concentration halfway between MDL and Estimated Quantitation Limit (4.74 ng/m^3).

d. Samples analyzed by ARB testing Laboratory Section Laboratory. Additional details on lab analysis available: http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/ethoamap.pdf. All of the "application site" sampling sites were adjacent to an 80 acre potato field. The ambient site data were collected at various areas adjacent to agricultural activity in Siskiyou County, CA.

e. Prevailing wind direction was generally from the Northwest.

6.2 Residential Bystander Post-Application Inhalation Risk Characterization

The ethoprop bystander volatilization inhalation exposure assessment compares the maximum and average air concentrations detected in each of the monitoring studies to the steady state HEC for residential bystanders, as no acute HEC is available for ethoprop. This comparison of the steady state HEC and the available application site monitoring data is a conservative representation of a potential resident who lives next to a treated field and may be exposed to the peak or average concentration of ethoprop volatilizing off the field over a 24-hour period. In addition, both the single peak air concentration per site and the arithmetic mean ethoprop air concentration from the ambient air monitoring study was compared to the steady-state HEC for residential bystanders. The comparison of the peak ambient concentrations against the steady state endpoint is a conservative representation of a potential resident of an agricultural area where ethoprop is being applied in multiple field locations.

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- The application site data were collected based on an application of a 10% granular formulation of ethoprop. There is uncertainty in extrapolating application site field measurements from the formulation applied in the study to the alternative EC formulation that is currently available on the market.

- Most of the data utilized in this preliminary assessment are 24-hour (or less) air samples. When these data are used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations at locations similar to the monitoring sites (i.e., the exposure and risk estimates assume an individual is outdoors all the time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations of ethoprop indoors. The assessment assumes that indoor concentrations will be at worst equivalent to outdoor concentrations and may potentially be lower.

- The available exposure data used for this analysis have been generated in California; however, ethoprop is used in many regions of the country. Therefore, the results based on the limited available air monitoring data were used to represent the rest of the country due to a lack of adequate information for any other region. It is unclear what potential impacts this extrapolation might have on the risk assessment. Factors such as meteorology and cultural practices may impact the overall amounts of ethoprop that volatilize from a treated field as well as the rate at which it volatilizes.

- The residential bystander estimated exposure should not be included in the human health risk assessment aggregate due to the fact that this is only a preliminary assessment and is not considered a refined assessment for the reasons noted above. There are limitations

associated with the air monitoring data that are available, such as the fact that most are air sampling and measurement techniques do not distinguish between aerosols and vapors. In addition, as noted in the above bullet, this assessment assumes residents are outdoors during the entire exposure duration.

6.3 Non-Occupational Spray Drift Exposures and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[15] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to <2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of ethoprop. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift® (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs)*.

For ethoprop, chemical-specific turf transferable residue (TTR) data are not available, therefore, the estimated TTR are based on a default assumption from the 2012 Residential SOPs that the transferable residue available for exposure is 1% of the total deposited residue, which is assumed to be equivalent to the maximum application rate.

A screening approach was developed based on the use of the AgDrift® model in situations where specific label guidance that defines application parameters is not available.[16] AgDrift® is

[15] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[16] http://www.agdrift.com/

appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift® was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Tables 8.0.1 and 8.0.2 provide the screening level drift related risk estimates for adults and children, respectively. In many cases, risk estimates are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to better characterize risk estimates related to drift, additional spray drift deposition fractions were also considered.

Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Ethoprop is registered on a variety of agricultural crops[17], and can be applied as an emulsifiable concentrate via enclosed cab groundboom equipment at application rates between 3 and 12 lbs ai/A. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for low boom height and using fine to medium/coarse spray type using the 90th percentile results.

The recommended drift scenario screening level option diverges from the default selection in the drift SOP based on the nature of the ethoprop emulsifiable concentrate applications (pre-plant) and the registered use sites. The default screening level options involves the "high boom" as the default scenario. As ethoprop is applied pre-plant to bare soil, the "low boom" spray type/nozzle configurations was selected to represent the screening level option for emulsifiable concentrate applications of ethoprop.

In addition to the screening level spray drift scenarios described above, additional results are provided using viable drift reduction technologies (DRTs). In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height and crop canopy conditions).

Dermal risk estimates were calculated for adults. For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4). Dermal and

[17] See Section 3.3 for additional detail on the full range of registered use sites and application rates

incidental oral risk estimates for children (1 to <2 years old) were combined because the toxicity endpoint for each route of exposure is the same (RBC AChE inhibition). The total applicable LOC is 1000, so MOEs <1000 represent risk estimates of concern.

Risk estimates related to spray drift are of concern at various distances from the edge of the field for adults and children (1 to <2 years) depending on the spray drift scenario. Adult and children risk estimates are summarized in Tables 6.3.1 and 6.3.2, respectively. For adults, the screening level scenario of low boom height and using fine to medium/coarse spray type requires a distance of over 300 feet to reach a dermal MOE ≥ 1000 for the range of crops assessed. For children, the screening level scenario also requires a distance of over 300 feet to reach a combined (dermal and incidental oral) MOE ≥1000 for the range of crops assessed. Drift reduction technologies, such as using coarser sprays and lowering boom height for groundboom sprayers, can reduce risk concerns. In the case of ethoprop, the screening scenario assumes a low boom height because of the use pattern (pre-plant applications). Regardless, there are still risk estimates of concern at the field edge. Further, chemical-specific TTR data could be submitted to help refine the spray drift assessment.

Table 6.3.1. Adult Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Ethoprop for the Dermal Route of Exposure.														
Crop/Rate Group	**Spray Type/ Nozzle Configuration[1]**	**Appl. Rate (lb ai/A)**	**TTR (ug/cm2)**	**At Edge**	**10 Feet**	**25 Feet**	**50 Feet**	**75 Feet**	**100 Feet**	**125 Feet**	**150 Feet**	**200 Feet**	**250 Feet**	**300 Feet**
Potatoes - west														
Groundboom	High Boom Very fine to Fine	12	**1.3338**	<1	<1	1	1	1	2	2	2	3	4	4
	Low Boom Very fine to Fine			<1	1	2	2	3	4	4	5	6	8	10
	High Boom Fine to Medium/Coarse			1	2	2	3	4	5	6	6	8	10	10
	Low Boom Fine to Medium/Coarse			1	3	4	5	6	8	10	10	16	16	16
Potatoes- east														
Groundboom	High Boom Very fine to Fine	9	**1.00035**	<1	<1	1	1	2	2	2	3	4	5	6
	Low Boom Very fine to Fine			<1	1	2	3	4	5	6	7	8	10	14
	High Boom Fine to Medium/Coarse			1	2	3	5	6	7	8	8	10	14	14
	Low Boom Fine to Medium/Coarse			1	3	5	7	8	10	14	14	21	21	21
Mint														
Groundboom	High Boom Very fine to Fine	4	**0.4446**	<1	1	2	3	4	5	5	7	8	12	13
	Low Boom Very fine to Fine			1	3	5	7	9	12	13	16	19	23	31
	High Boom Fine to Medium/Coarse			2	5	7	10	13	16	19	19	23	31	31
	Low Boom Fine to Medium/Coarse			3	8	12	16	19	23	31	31	47	47	47
Hops														

Table 6.3.1. Adult Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Ethoprop for the Dermal Route of Exposure.														
Crop/Rate Group	**Spray Type/ Nozzle Configuration[1]**	**Appl. Rate (lb ai/A)**	**TTR (ug/cm2)**	**At Edge**	**10 Feet**	**25 Feet**	**50 Feet**	**75 Feet**	**100 Feet**	**125 Feet**	**150 Feet**	**200 Feet**	**250 Feet**	**300 Feet**
Groundboom	High Boom Very fine to Fine	3	**0.33345**	1	1	2	4	5	6	7	9	11	16	18
	Low Boom Very fine to Fine			1	4	6	10	12	16	18	21	25	31	41
	High Boom Fine to Medium/Coarse			3	7	10	14	18	21	25	25	31	41	41
	Low Boom Fine to Medium/Coarse			4	10	16	21	25	31	41	41	62	62	62

1 - **Bolded** Spray type/nozzle configuration is the representative screening scenario for ethoprop

Table 6.3.2. Children (1<2 years old) Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Ethoprop for the Combined Dermal and Oral Routes of Exposure.														
Crop/Rate Group	**Spray Type/ Nozzle Configuration[1]**	**Appl. Rate (lb ai/A)**	**TTR (ug/cm2)**	**At Edge**	**10 Feet**	**25 Feet**	**50 Feet**	**75 Feet**	**100 Feet**	**125 Feet**	**150 Feet**	**200 Feet**	**250 Feet**	**300 Feet**
Potatoes - west														
Groundboom	High Boom Very fine to Fine	12	**1.3338**	<1	<1	<1	1	1	1	1	1	2	2	3
	Low Boom Very fine to Fine			<1	1	1	1	2	2	3	3	4	4	6
	High Boom Fine to Medium/Coarse			<1	1	1	2	3	3	4	4	4	6	6
	Low Boom Fine to Medium/Coarse			1	1	2	3	4	4	6	6	9	9	9
Potatoes- east														
Groundboom	High Boom Very fine to Fine	9	**1.00035**	<1	<1	<1	1	1	1	1	2	2	3	3
	Low Boom Very fine to Fine			<1	1	1	2	2	3	3	4	5	6	8
	High Boom Fine to Medium/Coarse			<1	1	2	3	3	4	5	5	6	8	8
	Low Boom Fine to Medium/Coarse			1	2	3	4	5	6	8	8	12	12	12
Mint														
Groundboom	High Boom Very fine to Fine	6	**0.4446**	<1	1	1	2	2	3	3	4	5	7	7
	Low Boom Very fine to Fine			1	2	3	4	5	7	8	9	11	13	17
	High Boom Fine to Medium/Coarse			1	3	4	6	8	9	11	11	13	18	17
	Low Boom Fine to Medium/Coarse			2	4	7	9	11	13	18	18	27	27	26
Hops														

Table 6.3.2. Children (1<2 years old) Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Ethoprop for the Combined Dermal and Oral Routes of Exposure.														
Crop/Rate Group	**Spray Type/ Nozzle Configuration[1]**	**Appl. Rate (lb ai/A)**	**TTR (ug/cm2)**	**At Edge**	**10 Feet**	**25 Feet**	**50 Feet**	**75 Feet**	**100 Feet**	**125 Feet**	**150 Feet**	**200 Feet**	**250 Feet**	**300 Feet**
Groundboom	High Boom Very fine to Fine	3	**0.33345**	<1	1	1	2	3	4	4	5	6	9	10
	Low Boom Very fine to Fine			1	2	4	5	7	9	10	12	14	18	24
	High Boom Fine to Medium/Coarse			1	4	5	8	10	12	14	14	18	24	24
	Low Boom Fine to Medium/Coarse			2	6	9	12	14	18	24	24	36	36	35

1 - **Bolded** Spray type/nozzle configuration is the representative screening scenario for ethoprop

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. The registered uses of ethoprop are not anticipated to result in a residential contribution to the aggregate risk assessment. Therefore, the aggregate assessment consists of dietary (food and drinking water) exposure and risk. In the case of ethoprop, since both the *food alone* and *water alone* dietary risk estimates exceed HED's level of concern, HED did not combine (i.e., aggregate) these exposure as the result would further exceed HED's level of concern. The acute and steady-state non-cancer dietary exposure estimates are detailed in Section 5.4.3 and 5.4.4.

Ethoprop is classified "likely to be carcinogenic to humans" based on malignant adrenal pheochromocytomas in male rats and is regulated with a Q_1*. Applying the Q_1* of 0.0281 $(mg/kg/day)^{-1}$ to the exposure value results in a cancer risk estimate of 7×10^{-6} for *food only*. For *water only*, the exposure value results in a cancer risk estimate of 5×10^{-5}.

Food only and *water only* dietary risk concerns are typically combined to estimate a dietary cancer risk assessment. The food only dietary cancer assessment is unrefined and based on tolerance level residues, default processing factors, and 100% crop treated assumptions. In the case of ethoprop, a dietary cancer risk for food and drinking water together (i.e., the aggregate cancer dietary assessment) was not completed because even though the *food only* cancer risk estimate could be refined, the water only cancer risk estimate drives the dietary cancer risk estimate. Refinements of the *water only* cancer risk estimates are not available at this time.

8.0 Cumulative Exposure/Risk Characterization

OPs, like ethoprop, share the ability to inhibit AChE through phosphorylation of the serine residue on the enzyme leading to accumulation of acetylcholine and ultimately cholinergic neurotoxicity. This shared MOA/AOP is the basis for the OP common mechanism grouping per OPP's *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999). The 2002 and 2006 CRAs used brain AChE inhibition in female rats as the source of dose response data for the relative potency factors and PODs for each OP, including ethoprop. Prior to the completion of Registration Review, OPP will update the OP CRA on AChE inhibition to incorporate new toxicity and exposure information available since 2006.

As described in Section 4.4, OPP has retained the FQPA Safety Factor for OPs, including ethoprop, due to uncertainties associated with neurodevelopmental effects in children and exposure to OPs. There is a lack of an established MOA/AOP for the neurodevelopment outcomes which precludes the agency from formally establishing a common mechanism group per the *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999) based on that outcome. Moreover, the lack of a recognized MOA/AOP and other uncertainties with exposure assessment in the epidemiology studies prevent the agency from establishing a causal relationship between OP exposure and neurodevelopmental outcomes. The agency will continue to evaluate the epidemiology studies

associated with neurodevelopmental outcomes and OP exposure prior to the release of the revised DRA. During this period, the agency will determine whether or not it is appropriate to apply the draft guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* for the neurodevelopment outcomes.

9.0 Occupational Exposure/Risk Characterization

9.1 Occupational Handler

Occupational handler exposure is anticipated from the registered uses of ethoprop. The occupational handler section is laid out in three sections. Section 9.1.1 addresses the ethoprop occupational handler non-cancer assessment based on surrogate unit exposure data. Section 9.1.2 addresses the non-cancer occupational handler assessment based on an available biomonitoring study. The ethoprop biomonitoring study was performed with the sole purpose of quantifying professional applicator exposure during the use of ethoprop in Pacific Northwest potato fields. As the original biomonitoring study occurred in a large portion of the occupational handler group for ethoprop occupational handlers in a discrete geographic location, there is uncertainty bridging the use of the data to other occupational handler groups with different agricultural practices and geographic variations. It is unclear how different agricultural and climate conditions would affect the resulting handler exposure estimates. **It is also important to note that individuals in the Washington State study often wore personal protective equipment beyond the label requirements, limiting personal exposures.** Section 9.1.3 addresses the occupational handler cancer assessment. Regardless of data source, non-cancer occupational handler risk estimates are of concern for ethoprop for mixer/loaders, loaders, and applicators for all handler scenarios assessed based on the LOC of 1,000.

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on current product labels, the scenarios which should serve as the basis for the quantitative exposure and risk assessment (cancer and non-cancer), are as follows:

- Loading granulars for tractor drawn spreader application;
- Mixing/loading EC (liquid) formulation for chemigation;
- Mixing/loading EC (liquid) formulation for groundboom application;
- Applying granules with a tractor drawn spreader;
- Loading/applying granules with a backpack spreader; and,
- Applying liquids with a groundboom sprayer.

The above exposure scenarios best represent the registered use pattern (i.e., soil incorporation of EC and granular end use formulations) for ethoprop.

9.1.1 Occupational Handler Exposure/Risk Estimates (Surrogate Unit Exposure Scenarios)

The potential absorbed doses and margins of exposure for ethoprop were calculated using standard EPA exposure algorithms and generic PHED/AHETF unit exposure values.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Assumptions and factors, as well as algorithms used to estimate non-cancer exposure and dose for occupational handlers are detailed in the most recent occupational and residential exposure (ORE) assessment memo (M. Lloyd; 09-15-2015; D421954).

The steady-state approach is appropriate for ethoprop given the toxicological and exposure profile. The steady-state endpoint selection for ethoprop overlaps with HED's traditional short-term exposure duration endpoint selection and is considered health protective for occupational handlers that apply commercially over longer periods of time (i.e., intermediate-term exposures).

The currently registered application rates for ethoprop generally range from 3 lbs ai/A to 12 lbs ai/A via ground application. The applications are specified to be conducted with engineering controls (lock-N-load equipment and closed cab applications), with the exception of backpack granular application for bananas. Typically, HED would also assess the use of handheld equipment, particularly for field grown ornamentals; however, currently registered ethoprop products prohibit the use of handheld equipment for treating field grown ornamentals and allow only ground-based application methods. The 15G product is the only registered ethoprop product that allows for backpack granular applications around the base of the banana tree that are then soil incorporated (presumably by hand by the loader/applicators). This particular application pattern requires use of double layer PPE, gloves, and PF10 respiratory protection. For the other registered uses, in addition to the engineering controls/closed system, mixer, loaders, applicators, and other handlers must also wear long sleeved shirt, long pants, shoes plus socks, chemical-resistant gloves, chemical-resistant apron (for mixing and loading), and protective eyewear.

For adults, when an endpoint is not sex-specific (i.e., the endpoints are based on developmental or fetal effects) a body weight of 80 kg is typically used in risk assessment; however, in this case, a female-specific body weight of 69 kg was used. While the endpoint of concern, RBC AChE inhibition, is not sex-specific, the female-specific body weight was used to protect for pregnant women due to uncertainty in the human dose-response relationship for neurodevelopmental effects (see Section 4.4).

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar, although there are separate dermal PODs for the different ethoprop formulations. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

HED relied on both chemical-specific biomonitoring data and surrogate unit exposure data in order to complete the ethoprop handler assessment. This section presents the risk estimates based on the surrogate unit exposure data. Risk estimates for the emulsifiable concentrate (EC) and granular (G) formulations are calculated separately because different dermal PODs were selected according to formulation type. All combined risk estimates are of concern for occupational

handler mixer/loaders, loaders, and applicators, assuming label-defined engineering controls.

For mixer/loaders using the label-defined engineering controls, total MOEs (dermal + inhalation) range from <1-11 for the liquid formulation and 19-190 for the granular formulation. For applicators using the label defined engineering controls, total MOEs range from <1-18 for the liquid formulation and 14-140 for the granular formulation, respectively. Of the evaluated exposure scenarios, the lowest combined MOEs are for mixing and loading for chemigation and groundboom application at application rates >5 lbs ai/A. Total non-cancer risk estimates are generally of greater concern (i.e., lower MOEs) for the liquid formulation than the granular formulation.

Tables 9.1.1.1 and 9.1.1.2 present the risk estimates for the ethoprop liquid and granular formulations, respectively based on surrogate or chemical-specific unit exposure data.

Table 9.1.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoprop [Liquid Formulation].								
Scenario[1]	**Representative Application/Crops**	**Application Rate (lbs ai/A)[2]**	**Area Treated (A/day)[3]**	**Dermal Dose (mg/kg/day)[4]**	**Dermal MOE[5] (LOC = 1000)**	**Inhalation Dose (mg/kg/day) [6]**	**Inhalation MOE[7] (LOC = 1000)**	**Total MOE[8] (LOC = 1000)**
Mixer/Loaders								
M/L liquids: Chemigation	Cabbage: Field crop, typical	5.1	350	0.223	**<1**	0.00214	**57**	**<1**
	Hops: Orchard	3		0.131	**1.2**	0.00126	**98**	**1.2**
	Potatoes (west): Field crop, high-acreage	12		0.523	**<1**	0.00506	**24**	**<1**
	Potatoes (east): Field crop, high-acreage	9		0.393	**<1**	0.00378	**33**	**<1**
	Sweet Potato: Field crop, typical	3.9		0.17	**<1**	0.00164	**75**	**<1**
M/L liquids: Groundboom	Cabbage: Field crop, typical	5.1	80	0.0509	**3.2**	0.000491	**250**	**3.2**
	Sweet Potato: Field crop, typical	3.9		0.0388	**4.2**	0.000375	**330**	**4.1**
	Field crop, typical	3		0.0299	**5.4**	0.000288	**430**	**5.3**
	Field Grown Ornamental Crops	3	40	0.0149	**11**	0.000144	**850**	**11**
	Field Grown Ornamental Crops	6		0.0299	**5.4**	0.000288	**430**	**5.3**
	Potatoes (west): Field crop, high-acreage	12	200	0.299	**0.54**	0.00288	**43**	**<1**
	Potatoes (east): Field crop, high-acreage	9		0.225	**0.72**	0.00216	**57**	**<1**
	Mint: Field crop, high-acreage	6		0.149	**1.1**	0.00144	**85**	**1.1**
Applicators								
	Cabbage: Field crop, typical	5.1	80	0.0301	**5.4**	0.000254	**480**	**5.3**

Table 9.1.1.1 Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoprop [Liquid Formulation].								
Scenario[1]	**Representative Application/Crops**	**Application Rate (lbs ai/A)[2]**	**Area Treated (A/day)[3]**	**Dermal Dose (mg/kg/day)[4]**	**Dermal MOE[5] (LOC = 1000)**	**Inhalation Dose (mg/kg/day) [6]**	**Inhalation MOE[7] (LOC = 1000)**	**Total MOE[8] (LOC = 1000)**
Applicator: liquid sprays	Sweet Potato: Field crop, typical	3.9		0.023	**7**	0.000194	**630**	**6.9**
	Field crop, typical	3		0.0177	**9.2**	0.000149	**830**	**9.1**
	Field Grown Ornamental Crops	3	40	0.00887	**18**	0.0000748	**1600**	**18**
	Potatoes (west): Field crop, high-acreage	12	200	0.177	**0.92**	0.00149	**83**	**<1**
	Potatoes (east): Field crop, high-acreage	9		0.133	**1.2**	0.00112	**110**	**1.2**
	Mint: Field crop, high-acreage	6		0.0887	**1.8**	0.000748	**160**	**1.8**

1 Engineering Control Unit Exposures for each exposure scenario based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (**[March, 2013]**); Level of mitigation: Eng. Controls.
2 Based on registered labels (Reg. No. 5481-9041/5481-9040/5481-9042).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated (A/day) ÷ BW (69 kg).
5 Dermal MOE = Dermal $BMDL_{10}$ (0.1625 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated (A/day) ÷ BW (69 kg).
7 Inhalation MOE = Inhalation $BMDL_{10}$ (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). HEDs = 0.035 mg/kg/day (8.3L/min); 0.071 mg/kg/day (16.7 L/min); 0.123 mg/kg/day (29 L/min)
8 Total MOE = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE). LOC = 1,000

Table 9.1.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulations].								
Scenario	**Representative Application/Crops**	**Application Rate (lbs ai/A)**	**Area Treated (A/day)**	**Dermal Dose (mg/kg/day)**	**Dermal MOE (LOC = 1000)**	**Inhalation Dose (mg/kg/day)**	**Inhalation MOE (LOC = 1000)**	**Total MOE (LOC = 1000)**
Loaders								
Tractor-drawn spreader	Field crop, typical	3	80	0.0299	350	0.000288	**430**	**190**
	Sweet potato: Field crop, typical	3.9		0.0388	270	0.000375	**330**	**150**
	Cabbage: Field crop, typical	5.1		0.0509	200	0.000491	**250**	**110**
	Tobacco: Field crop, typical	6		0.0599	**170**	0.000577	**210**	**94**

Table 9.1.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulations].								
Scenario	**Representative Application/Crops**	**Application Rate (lbs ai/A)**	**Area Treated (A/day)**	**Dermal Dose (mg/kg/day)**	**Dermal MOE (LOC = 1000)**	**Inhalation Dose (mg/kg/day)**	**Inhalation MOE (LOC = 1000)**	**Total MOE (LOC = 1000)**
	Beans: Field crop, typical	8.1		0.0807	**130**	0.00078	**160**	**72**
	Corn: Field crop, high-acreage	3	200	0.0748	**140**	0.000722	**170**	**77**
	Corn: Field crop, high-acreage	4		0.0997	**100**	0.000962	**130**	**57**
	Mint: Field crop, high-acreage	6		0.149	**70**	0.00144	**85**	**38**
	Potatoes (east): Field crop, high-acreage	9		0.225	**46**	0.00216	**57**	**25**
	Potatoes (west): Field crop, high-acreage	12		0.299	**35**	0.00288	**43**	**19**
Applicators								
Applicator: broadcast granules	Field crop, typical	3	80	0.00696	1500	0.000765	**160**	**140**
	Field crop, typical	4		0.00928	1100	0.00102	**120**	**110**
	Cabbage: Field crop, typical	5.1		0.0118	**880**	0.0013	**95**	**86**
	Tobacco: Field crop, typical	6		0.0139	**750**	0.00154	**80**	**72**
	Beans: Field crop, typical	8.1		0.0188	**550**	0.00207	**59**	**53**
	Corn: Field crop, high-acreage	3	200	0.0174	**600**	0.00191	**64**	**58**
	Corn: Field crop, high-acreage	4		0.0232	**450**	0.00255	**48**	**43**
	Sugarcane: Field crop, high-acreage	5.88		0.0341	**300**	0.00375	**33**	**30**
	Mint: Field crop, high-acreage	6		0.0348	**300**	0.00383	32	**29**
	Potatoes (east): Field crop, high-acreage	9		0.0522	**200**	0.00574	**21**	**19**

Table 9.1.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulations].								
Scenario	**Representative Application/Crops**	**Application Rate (lbs ai/A)**	**Area Treated (A/day)**	**Dermal Dose (mg/kg/day)**	**Dermal MOE (LOC = 1000)**	**Inhalation Dose (mg/kg/day)**	**Inhalation MOE (LOC = 1000)**	**Total MOE (LOC = 1000)**
	Potatoes (west): Field crop, high-acreage	12		0.0696	**150**	0.00765	**16**	**14**
Loader/Applicators								
Backpack application	Banana: Orchard	121	1	.127	**82**	0.0042	**17**	**16**

1 Engineering Control Unit Exposures for each exposure scenario based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (**[March, 2013]**); Level of mitigation: Eng. Controls, except for Loader/applicator: backpack applications.
2 Based on registered labels (Reg. No. 5481-9041/5481-9040/5481-9042).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (69 kg).
5 Dermal MOE = Dermal $BMDL_{10}$ (10.4 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre) × Area Treated (A/day) ÷ BW (69 kg).
7 Inhalation MOE = Inhalation $BMDL_{10}$ (mg/kg/day) ÷ Inhalation Dose (mg/kg/day). HEDs = 0.035 mg/kg/day (8.3L/min); 0.071 mg/kg/day (16.7 L/min); 0.123 mg/kg/day (29 L/min)
8 Total MOE = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE).

9.1.2 Occupational Handler Exposure/Risk Estimates (Based on Biomonitoring Data)

Occupational Handler Exposure Data and Assumptions

The observational biomonitoring study (MRID 45621501) used the Mocap® 6EC formulation [EPA Reg. No. 5481-09041] of ethoprop with mechanical ground application equipment to treat potato fields in the Central Basin of Washington State in the United States. This study was used in multiple previous HED risk assessments[18], which

[18] Dawson, 2005; D281648 / Lloyd, 2010, D375925

assessed exposure from the application of ethoprop on potatoes for handlers in the Northwest and also extrapolated the biomonitoring results to similar crop/application patterns. The application methodology on the registered labels is substantively similar to the application equipment used in the biomonitoring study (i.e., closed cab tractors pulling sweep injection booms followed by rotary cultivators and specialized groundboom rigs for surface spray applications). A complete characterization of the biomonitoring study is detailed in the most recent occupational and residential exposure (ORE) assessment memo (M. Lloyd; 09-15-2015; D421954).

Chemical-specific handler exposure data are available to support this registration review assessment. HED evaluated the potential exposure to ethoprop using urinary concentrations of M1 (O-ethyl-S-propylphosphorothioate), as an exposure biomarker in the available biomonitoring study. Occupational handler risk estimates were calculated using the biological monitoring data in two distinct manners: (1) a daily dose approach; and (2) a cumulative dose approach. While the individual results varied widely, risk estimates from both approaches result in risk estimates of concern (i.e, MOEs below the LOC of 1,000).

The biomonitoring study data are appropriate to bridge for the currently registered ethoprop use patterns registered with both the emulsifiable concentrate (for the ethoprop MOCAP® EC formulation) and the two granular formulations (15G and 20G), although the results should be interpreted with caution because individuals in the Washington State study often wore personal protective equipment beyond the label requirements, that are consistent with climates conditions in the Pacific Northwest. The biomonitoring risk estimates are scaled to the various registered rates for the EC formulation. For the granular formulations, the risk estimate results are extrapolated from the EC formulation (in the study) to the existing granular formulation and scaled to the various registered rates for the granular formulations. The formulation extrapolation is appropriate and conservative based on the toxicity information available for ethoprop. In this biomonitoring study, it is not possible to parse the occupational handler exposure contribution by route (i.e, dermal, inhalation). While the same oral endpoint and point of departure (a $BMDL_{10}$ POD of 0.065 mg/kg/day based on inhibition of red blood cell cholinesterase[19]) is used for both the emulsifiable concentrate and granular formulations, examining the difference between the route-specific points of departure can help characterize the conservatism of extrapolating the emulsifiable concentrate results to the granular formulation.
The occupational handler assessment relies on the same steady-state inhalation endpoint and point of departure for the emulsifiable concentrate and granular formulation, while the steady-state dermal points of departure are different for the two formulations. The effect is the same (inhibition of red blood cell cholinesterase) for both formulations, although the point of departure is 65x lower[20] for the granular formulation versus the emulsifiable concentration. Studies have shown that farmworkers receive the bulk of their potential pesticide exposure through the dermal route of exposure[21]. Based on the differential toxicity between the two formulations and the lower exposure profile of occupational handlers using granular formulations, HED finds it appropriate and conservative to extrapolate the results of the available biomonitoring study from the emulsifiable concentrate (monitored in the study) to the granular formulation.

[19] See Table 4.5.4.2 for additional detail
[20] See Table 3.2 – POD of 0.1625 mg/kg/day for the EC formulation vs. 10.4 mg/kg/day for granular
[21] Available: [Spear et al., 1977; Popendorf et al., 1979; Davis et al., 1982, 1983; Everhart and Holt, 1982; Herman et al., 1985]; http://onlinelibrary.wiley.com/doi/10.1002/ajim.1122/pdf

All of the risk estimates based on the biomonitoring data reflect the use of engineering controls **plus the use of additional PPE reflected in the biomonitoring study report**. HED analyzed the ethoprop biomonitoring data by scaling the calculated daily dose and cumulative dose (in mg/kg/day) from the application rate applied in the biomonitoring study based on the existing application rates (2.1 to 12 lbs ai/A) on the product label. MOEs calculated from the arithmetic mean daily exposure for mixer/loaders are of concern for each individual (days 1-4). Mixer/loader MOEs ranged from 9-36, based on single day output for the higher application rates. For applicators, MOEs calculated from the arithmetic mean daily exposure for applicators are also of concern on any individual day (MOEs range from 34-210 for days 1-4. For mixer/loader/applicators (where individuals monitored in the study completed a variety of job tasks) MOEs calculated from the arithmetic mean daily exposure for that job category were also of concern. Mixer/loader/applicator MOEs ranged from 9 – 64 for the highest registered ethoprop application rate.

For all application rates, MOEs calculated from the cumulative doses are of concern for each occupational handler group [mixer/loader, applicator, mixer/loader/applicator] with MOEs ranging from 4-83, depending on the job activity and application rate.

Table 9.1.2.1. Risk Estimates For Ethoprop Handlers Based On Daily And Cumulative Dose Estimates From MRID 45621501.

Occupational Handler Monitoring Category	Margins of Exposure (MOEs) Based On Single Day & Cumulative [M1] In Urine[4] (LOC = 1000)				
	Day 1	Day 2	Day 3	Day 4	Cumulative
Based on ethoprop[5] scaled to 3 lbs ai/A					
Mixer/Loader[1]	35	58	140	76	15
Applicators[2]	850	140	580	560	83
Mixer/Loader/Applicators[3]	260	53	35	61	14
Based on ethoprop[5] scaled to 4 lbs ai/A					
Mixer/Loader[1]	26	43	110	57	11
Applicators[2]	640	100	430	420	62
Mixer/Loader/Applicators[3]	650	260	480	430	83
Based on ethoprop[5] scaled to 5.1 lbs ai/A					
Mixer/Loader[1]	21	34	84	45	9
Applicators[2]	500	80	340	330	49
Mixer/Loader/Applicators[3]	150	31	21	36	8
Based on ethoprop[5] scaled to 6 lbs ai/A					
Mixer/Loader[1]	18	29	72	38	8
Applicators[2]	420	68	290	280	41
Mixer/Loader/Applicators[3]	130	27	18	30	7
Based on ethoprop[5] scaled to 9 lbs ai/A					
Mixer/Loader[1]	12	19	48	25	5
Applicators[2]	280	45	190	190	28
Mixer/Loader/Applicators[3]	85	18	12	20	5
Based on ethoprop[5] scaled to 12 lbs ai/A					

Table 9.1.2.1. Risk Estimates For Ethoprop Handlers Based On Daily And Cumulative Dose Estimates From MRID 45621501.					
Occupational Handler Monitoring Category	**Margins of Exposure (MOEs) Based On Single Day & Cumulative [M1] In Urine[4] (LOC = 1000)**				
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Cumulative**
Mixer/Loader[1]	9	14	36	19	4
Applicators[2]	210	34	140	140	21
Mixer/Loader/Applicators[3]	64	13	9	15	4

1 – Mixer/Loader = Margin of Exposure calculated from Arithmetic mean exposure of study participants (ML1, ML2, ML3, AP11).
2 – Applicators = Margin of Exposure calculated from Arithmetic mean exposure of study participants (AP6, AP12, AP14).
3 – Mixer/Loader/Applicators = Margin of Exposure calculated from Arithmetic mean exposure of study participants (AP1, AP2, AP3, AP4, AP5 AP13, AP15, AP16, AP17, AP18, AP19, AP20, AP21, AP22, AP24). *AP1 Urines were also collected on days 5 & 6. AP2 urine was also collected on Day 5. MOEs are not presented here.
4 – MOEs calculated per exposure day and with cumulative 4 day exposure based on inhibition of RBC AChE in adult male rats; POD = $BMDL_{10}$=0.065 mg/kg/day.
5- In the biomonitoring study, MOCAP EC . See Section 9.1.2 for additional information

The MOEs calculated from the daily doses in the biomonitoring study ranged widely among individual handlers. The Agency believes that these results are to be expected when considering the actual work practices of multiple individuals monitored over several days. The hazard concerns are a key driver of occupational risk from handling the liquid formulation of ethoprop. The study screened for very low levels of exposure (i.e., low ppb); therefore, the smallest increase in exposure significantly affected (lowered) the risk estimate (MOE). The level of care with which an individual handles a pesticide greatly influences the overall exposure to the pesticide. Given this study monitored the actual work practices of 23 handlers, degrees of caution will differ.

The exposure data from the biological monitoring study (MRID #45621501) on users in Washington State potato fields is appropriate to be bridged to the existing registered uses. The ethoprop biomonitoring study was performed with the sole purpose of quantifying professional applicator exposure during the use of ethoprop in Pacific Northwest potato fields. As the original biomonitoring study occurred in a large portion of the occupational handler group for ethoprop occupational handlers in a discrete geographic location, there is uncertainty bridging the use of the data to other occupational handler groups with different agricultural practices and geographic variations. It is unclear how different agricultural and climate conditions would affect the resulting handler exposure estimates. **It is also important to note that individuals in the Washington State study often wore personal protective equipment beyond the label requirements, limiting personal exposures.** This is an important detail to consider when interpreting the biomonitoring results.

The study protocol required that potential adverse effects of ethoprop be explained to each of the study participants. The study report provides detailed descriptions of observations by the study monitors of both the workers' work practices and other observations. There is no mention of any worker exhibiting any adverse effects or anything that would be suggestive of cholinergic clinical signs in the original biomonitoring study. It is important when interpreting the results of this study to note that approximately 50 percent of the samples collected were less than the quantification limit. Application rates in the original study ranged from 4-12 lbs ai/A (i.e., comparable with the range of the currently registered ethoprop labels).

There is one additional risk characterization piece to consider as it relates to biological monitoring. HED evaluated Washington State's annual cholinesterase monitoring report for 2013[22]. Washington State evaluates a number of agricultural chemicals that can result in cholinesterase inhibition; ethoprop is among those that have been monitored. The report is valuable because Washington State represents:

1) an area with both high overall usage of both formulations of ethoprop (granular and EC);
2) a region that represents multiple crops where ethoprop is applied; and
3) a region with a high percentage of the highest application rate of ethoprop (12 lbs ai/A).

The report highlighted a few important pieces of information that relate to the risk characterization for ethoprop use:

- Only 6% of handlers (n=1994) had cholinesterase depression (from any OP/n-methyl carbamate).
- No handlers reported pesticide illness/symptoms in 2013.
- Only 4% (n=9) had cholinesterase depression to the point of "exposure removal" level defined by WA state.
- Only 2% (n=2) had cholinesterase depression to the point of "work evaluation" level defined by WA state.
- The 2013 WA state results are in line with annual monitoring results since 2008.

Unfortunately, the Washington State program does not differentiate the individual agricultural chemicals where worker exposure may have occurred. Still, even if one was to assume that all the adverse incidents identified in the 2013 results of the Washington State program were due to ethoprop exposure, the overall report provides another line of evidence that, at least in the Pacific Northwest where monitoring takes place, that workers are not exposed to ethoprop to the point of cholinesterase depression.

9.1.3 Occupational Handler Exposure/Risk Estimates (Cancer Risk Estimation)

9.1.3.1 Occupational Handler Cancer Risk Estimates (Standard LADD Approach)

Occupational Handler Cancer Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler cancer risk assessments. Assumptions and factors, as well as algorithms used to estimate the cancer exposure and dose for occupational handlers are detailed in the most recent occupational and residential exposure (ORE) assessment memo (M. Lloyd; 09-15-2015; D421954).

One point that departs from standard cancer assessment practices is noteworthy for the human health risk assessment. The majority of applications of ethoprop are restricted to 1 application per year, and HED typically assesses "private" and "commercial" applicators at 10 and 30 days per year, respectively. HED worked in consultation with BEAD and PRD to refine the default "private" and "commercial" handler days per year of exposure input for Pacific Northwest potatoes to 5 and 8 days per year, respectively. Complete details on deriving the refinements can be found in the BEAD memo, "BEAD Estimates for Applicator Exposure to Ethoprop From Applications Made to Potatoes in the Pacific Northwest".

[22] Available: http://www.lni.wa.gov/Safety/Topics/AtoZ/Cholinesterase/files/2013Report.pdf

Rate Information for use in Cancer Risk Assessment:
For the occupational handler cancer risk assessment, HED consulted with BEAD and obtained seasonal average application rate information. Seasonal average application rates are appropriate for use in the cancer risk assessment because the assessment assumes use every year over a 30 year working lifetime. Where seasonal rate information was not available, HED used the average of the high and low application rates for each crop presented on the label. Since ethoprop is used as both an insecticide and a nematicide, occupational handler cancer risk estimates are presented for both cases to help risk managers identify the potential range in the cancer risk estimates for each crop. Additional detail on the rate information used in the cancer assessment is detailed in the ORE disciplinary memo (M. Lloyd; 09-15-2015; D421954).

Summary of Occupational Handler Cancer Exposure and Risk Estimates

Cancer risk estimates resulting from exposures to ethoprop were calculated using a linear low-dose extrapolation approach in which a *Lifetime Average Daily Dose* (LADD) is first calculated and then compared with a Q_1^* that has been calculated for ethoprop based on dose response data ($Q_1^* = 2.8 \times 10^{-2}$ (mg/kg/day)$^{-1}$).

Tables 9.1.3.1.1 and 9.1.2.1.2 summarize the occupational handler cancer assessment for the emulsifiable concentrate and granular formulations, respectively. The quantitative cancer risk assessment also calculated separate cancer risk assessment estimates for the liquid and granular formulations, for both private handlers and commercial handlers, respectively. All of the cancer risk estimates presented reflect the use of engineering controls except the loader/applicator for backpack granule application for bananas; the range in the cancer risk estimates considers the typical application rate per crop and formulation. For the emulsifiable concentrate formulation, the private handler cancer risk estimates range from 3.5×10^{-6} to 9.6×10^{-5} for mixer/loaders and 2.0×10^{-6} to 3.2×10^{-5} for applicators. The commercial handler cancer risk estimates range from 1.0×10^{-5} to 2.9×10^{-4} for mixer/loaders and 6.1×10^{-6} to 9.7×10^{-5} for applicators. For the granular formulation, the private handler cancer risk estimates ranged from 3.9×10^{-6} to 5.5×10^{-5} for mixer/loaders and 1.0×10^{-6} to 1.4×10^{-5} for applicators. The commercial handler cancer risk estimates ranged from 1.2×10^{-5} to 1.7×10^{-4} for mixer/loaders and 3.0×10^{-6} to 4.2×10^{-5} for applicators.

Typically, cancer risk estimates that are not based on the use of engineering controls present a range of risk estimates to reflect increasing PPE and/or the use of engineering controls. In the case of the backpack granular application for bananas, the cancer risk estimates reflects the current label PPE. Based on the available surrogate exposure data for that exposure scenario, no additional PPE is available for that exposure scenario. Additionally, the use of engineering controls is not available for the granular application to banana trees.

Table 9.1.3.1.1 Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Liquid Formulation].									
Crop or Target	**Exposure Scenario**	**Private Handler**				**Commercial Handler**			
		LADD (mg/kg/day)		**Total LADD[3]**	**Cancer Risk Estimate[4]**	**LADD (mg/kg/day)**		**Total LADD[3]**	**Cancer Risk Estimate[4]**
		Dermal[1]	**Inhalation[2]**			**Dermal[1]**	**Inhalation[2]**		
Hops: Orchard	M/L: Chemigation 2.3 lbs ai/A	0.00106	0.000010	0.0011	3.0E-05	0.0032	0.0000308	0.0032	9.1E-05
Cabbage: Field crop, typical	M/L: Chemigation 3.7 lbs ai/A	0.00171	0.000017	0.0017	4.8E-05	0.0051	0.0000494	0.0052	1.5E-04
Sweet Potato: Field crop, typical	M/L: Chemigation 3.5 lbs ai/A	0.00161	0.000016	0.0016	4.6E-05	0.0048	0.0000472	0.0049	1.4E-04
Potatoes: Field crop, high-acreage	M/L: Chemigation 4.5 lbs ai/A	0.00104	0.0000101	0.00105	3.0E-05	0.00166	0.0000161	0.00168	4.7E-05
Potatoes: Field crop, high-acreage	M/L: Chemigation 7.3 lbs ai/A	0.00169	0.0000163	0.00171	4.8E-05	0.0027	0.0000261	0.00273	7.7E-05
Cabbage: Field crop, typical	M/L: Groundboom 3.7 lbs ai/A	0.0004	0.00000	0.000374	1.1E-05	0.0011	0.00001	0.00112	3.2E-05
Sweet Potato: Field crop, typical	M/L: Groundboom 3.5 lbs ai/A	0.0004	0.00000	0.000396	1.1E-05	0.0012	0.00001	0.00119	3.3E-05
Field Grown Ornamental Crops	M/L: Groundboom 2.3 lbs ai/A	0.000111	0.00000107	0.000112	3.2.E-06	0.000333	0.00000321	0.000336	9.4.E-06
Potatoes: Field crop, high-acreage [	M/L: Groundboom 4.5 lbs ai/A	0.000595	0.00000574	0.000601	1.7E-05	0.000952	0.00000919	0.000961	2.7E-05
Potatoes: Field crop, high-acreage	M/L: Groundboom 7.3 lbs ai/A	0.000971	0.00000928	0.000983	2.8E-05	0.00155	0.0000149	0.00157	4.4E-05
Mint: Field crop, high-acreage	M/L Groundboom 4.5 lbs ai/A	0.00119	0.000012	0.0012	3.4E-05	0.0036	0.0000344	0.0036	1.0E-04

Table 9.1.3.1.1 Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Liquid Formulation].									
Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Field Grown Ornamental Crops	Applicator Groundboom 2.3 lbs ai/A	0.0000658	0.000000554	0.0000664	1.9.E-06	0.000197	0.00000166	0.000199	5.6.E-06
Cabbage: Field crop, typical	Applicator Groundboom 3.7 lbs ai/A	0.00023	0.000002	0.0002	6.6E-06	0.0007	5.86E-06	0.0007	2.0E-05
Sweet Potato: Field crop, typical	Applicator Groundboom 3.5 lbs ai/A	0.00022	0.000002	0.0002	6.3E-06	0.0007	5.53E-06	0.0007	1.9E-05
Potatoes: Field crop, high-acreage [insecticide]	Applicator: Groundboom 4.5 lbs ai/A	0.000353	0.00000298	0.000356	1.0E-05	0.000565	0.00000476	0.000569	1.6E-05
Potatoes: Field crop, high-acreage [nematicide]	Applicator Groundboom 7.3 lbs ai/A	0.000572	0.00000483	0.000577	1.6E-05	0.000916	0.00000772	0.000923	2.6E-05
Mint: Field crop, high-acreage	Applicator 4.5 lbs ai/A	0.00071	0.000006	0.0007	2.0E-05	0.0021	0.0000179	0.0021	6.0E-05

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (10/30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 2.81 \times 10^{-2}$ $(mg/kg/day)^{-1}$.

Table 9.1.3.1.2. Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulation].									
Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Sweet potato: Field crop, typical	M/L: Tractor Spreader 3.5 lbs ai/A	0.0004	0.000004	0.000374	1.1E-05	0.0011	0.00001	0.00112	3.2E-05
Cabbage: Field crop, typical	M/L: Tractor Spreader	0.0004	0.000004	0.000396	1.1E-05	0.0012	0.00001	0.00119	3.3E-05

Table 9.1.3.1.2. Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulation].									
Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
	3.7 lbs ai/A								
Tobacco: Field crop, typical	M/L: Tractor Spreader 5.7 lbs ai/A	0.0006	0.000006	0.000609	1.7E-05	0.0018	0.00002	0.00183	5.1E-05
Beans (Snap, etc): Field crop, typical	M/L: Tractor Spreader 2.2 lbs ai/A	0.0002	0.000002	0.000235	6.6E-06	0.0007	0.00001	0.000704	2.0E-05
Beans (Snap, etc): Field crop, typical	M/L: Tractor Spreader 2.8 lbs ai/A	0.0003	0.000003	0.000299	8.4E-06	0.0009	0.00001	0.000896	2.5E-05
Beans (Dry/Pea): Field crop, typical	M/L: Tractor Spreader 3 lbs ai/A	0.0003	0.000003	0.00032	9.0E-06	0.0010	0.00001	0.000959	2.7E-05
Mint: Field crop, high-acreage	M/L: Tractor Spreader 4.5 lbs ai/A	0.0012	0.000012	0.0012	3.4E-05	0.0036	0.00003	0.0036	1.0E-04
Potatoes: Field crop, high-acreage	M/L: Tractor Spreader 4.5 lbs ai/A	0.000595	0.00000574	0.000601	1.7E-05	0.000952	0.00000919	0.000961	2.7E-05
Potatoes: Field crop, high-acreage	M/L: Tractor Spreader 7.3 lbs ai/A	0.000971	0.00000928	0.000983	2.8E-05	0.00155	0.0000149	0.00157	4.4E-05
Sugarcane: Field crop, high-acreage	M/L: Tractor Spreader 4 lbs ai/A	0.0011	0.000010	0.00107	3.0E-05	0.0032	0.00003	0.0032	9.0E-05
Sweet corn: Field crop, typical [insecticide use]	M/L: Tractor Spreader 1.3 lbs ai/A	0.0001	0.000001	0.000139	3.9E-06	0.0004	0.00000	0.000417	1.2E-05
Sweet corn: Field crop, typical [nematicide use]	M/L: Tractor Spreader 2.3 lbs ai/A	0.0002	0.000002	0.000246	6.9E-06	0.0007	0.00001	0.000738	2.1E-05

Table 9.1.3.1.2. Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulation].									
Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Sweet corn: Field crop, typical [insecticide use]	Applicator: Tractor Spreader 1.3 lbs ai/A	0.0000	0.000004	0.0000355	1.0E-06	0.0001	0.00001	0.000107	3.0E-06
Sweet corn: Field crop, typical [nematicide use]	Applicator: Tractor Spreader 2.3 lbs ai/A	0.0001	0.000006	0.0000628	1.8E-06	0.0002	0.00002	0.000188	5.3E-06
Sugarcane: Field crop, high-acreage	Applicator 4 lbs ai/A	0.0002	0.000027	0.000273	7.7E-06	0.0007	0.00008	0.000819	2.3E-05
Mint: Field crop, high-acreage	Applicator 4.5 lbs ai/A	0.0003	0.000031	0.000307	8.6E-06	0.0008	0.00009	0.000922	2.6E-05
Potatoes: Field crop, high-acreage	Applicator 4.5 lbs ai/A	0.000138	0.0000152	0.000154	4.3E-06	0.000221	0.0000244	0.000246	6.9E-06
Potatoes: Field crop, high-acreage	Applicator 7.3 lbs ai/A	0.000224	0.0000246	0.000249	7.0E-06	0.000359	0.0000394	0.000398	1.1E-05
Beans (Dry/Pea): Field crop, typical	Applicator: Tractor Spreader 3 lbs ai/A	0.0001	0.000008	0.0000819	2.3E-06	0.0002	0.00002	0.000246	6.9E-06
Sweet potato: Field crop, typical	Applicator: Tractor Spreader 3.5 lbs ai/A	0.0001	0.000009	0.0000955	2.7E-06	0.0003	0.00003	0.000287	8.1E-06
Cabbage: Field crop, typical	Applicator: Tractor Spreader 3.7 lbs ai/A	0.0001	0.000010	0.000101	2.8E-06	0.0003	0.00003	0.000303	8.5E-06
Tobacco: Field crop, typical	Applicator: Tractor Spreader 5.7 lbs ai/A	0.0001	0.000015	0.000156	4.4E-06	0.0004	0.00005	0.000468	1.3E-05
Beans (Snap, etc): Field crop, typical	Applicator: Tractor Spreader 2.2 lbs ai/A	0.0001	0.000006	0.00006	1.7E-06	0.0002	0.00002	0.00018	5.1E-06

Table 9.1.3.1.2. Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Granular Formulation].									
Crop or Target	**Exposure Scenario**	**Private Handler**				**Commercial Handler**			
		LADD (mg/kg/day)		**Total LADD[3]**	**Cancer Risk Estimate[4]**	**LADD (mg/kg/day)**		**Total LADD[3]**	**Cancer Risk Estimate[4]**
		Dermal[1]	**Inhalation[2]**			**Dermal[1]**	**Inhalation[2]**		
Beans (Snap, etc): Field crop, typical	Applicator: Tractor Spreader 2.8 lbs ai/A	0.0001	0.000008	0.0000765	2.2E-06	0.0002	0.00002	0.000229	6.4E-06
Banana/plantain: orchard[5]	Loader/applicator 90.8 lbs ai/A	.001	0.0000332	0.000242	3.0.E-05	0.003	0.0000996	0.00314	8.8E-05

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (10/30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure 35 (yrs) ÷ Lifetime expectancy (78 yrs)].

2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (10/30days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy 78 (yrs)].

3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).

4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 2.81 \times 10^{-2}$ $(mg/kg/day)^{-1}$

5 Reflects Double Layer PPE with gloves, & a PF10 respirator; not engineering controls like the other scenarios assessed

9.1.3.2 Occupational Handler Cancer Risk Estimates (Based on Biomonitoring Data)

While HED's standard cancer assessment risk estimates are detailed in Section 9.1.3.1, a cancer risk estimate screen can also be performed based on the worker exposure profile from the biomonitoring study outlined in Section 9.1.2. For the same reasons identified in Section 9.1, it is appropriate to consider this occupational handler cancer risk estimation based on both the granular and EC formulations, with the caveats about the use of extra PPE in the study.

Summary of Occupational Handler Cancer Exposure and Risk Estimates

Table 9.1.3.2.1 summarize the occupational handler cancer assessment based on the biomonitoring study. All of the cancer risk estimates presented reflect the use of engineering controls **plus the use of additional PPE reflected in the biomonitoring study report**. While current label requirements indicate engineering controls are required, the biomonitoring study report details a number of additional PPE items worn by study subjects including Tyvek suits, coveralls, hats, and various head coverings.

The private handler cancer risk estimates range from 3.2×10^{-6} to 5.2×10^{-6} for mixer/loaders and 8.3×10^{-7} to 1.3×10^{-6} for applicators, depending on the crop/rate combination. The commercial handler cancer risk estimates range from 9.6×10^{-6} to 1.6×10^{-5} for mixer/loaders and 2.5×10^{-6} to 4.0×10^{-6} for applicators depending on the crop/rate combination. The mixer/loader scenarios for both crop/rate combinations are in the cancer risk estimate range between 1×10^{-6} and 1×10^{-4}.

Table 9.1.3.2.1. Occupational Handler Cancer Exposure and Risk Estimates for Ethoprop [Biomonitoring Screen].

Crop or Target	Exposure Scenario	Private Handler		Commercial Handler	
		Total LADD (mg/kg/day)[3]	Cancer Risk Estimate[4]	Total LADD (mg/kg/day)	Cancer Risk Estimate[4]
Potatoes	M/L: 7.3 lbs ai/A	0.00018	5.2E-06	0.00055	1.6E-05
Potatoes	Applicator: 7.3 lbs ai/A	0.00005	1.3E-06	0.00014	4.0E-06
Mint	M/L: 4.5 lbs ai/A	0.00011	3.2E-06	0.00034	9.6E-06
Mint	Applicator: 4.5 lbs ai/A	0.00003	8.3E-07	0.00009	2.5E-06

The above occupational cancer risk estimates are based on data derived from the biomonitoring study; specifically, the use of engineering controls plus the use of additional dermal PPE (e.g., Tyvek suits, coveralls, head coverings). Therefore, these results cannot be directly compared with the standard cancer risk estimates presented in Section 9.1.3.1. Additionally, because the study monitoring units had differential exposure based on the number of ethoprop uses over the course of monitoring, the highest cumulative dose per worker group (M/L and applicators) was used as a surrogate for the average daily dose (ADD). There are other potential surrogates for the ADD such as 1) the highest single dose per individual per worker group, or 2) the arithmetic mean exposure per worker group. HED selected the highest cumulative dose value per worker group as the surrogate for ADD because of the uncertainties surrounding the kinetics of the M1 metabolite and the extrapolation of 4 days of exposure (in the biomonitoring study) to a seasonal and then lifetime exposure estimation.

9.2 Occupational Post-application Exposure/Risk Estimates

9.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010[23]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis[24]. During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies) or further analysis is required for ethoprop.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by ARTF. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

A summary of the non-occupational bystander post-application inhalation exposure assessment for ethoprop is detailed in Section 6.1.

9.2.2 Occupational Post-Application Dermal Exposure/Risk Estimates

A quantitative post-application dermal exposure assessment has not been conducted for ethoprop because ethoprop is typically applied pre-plant/pre-emergent in the growing season. Ethoprop is used in pre-plant and pre-emergent applications and is normally soil incorporated or watered-in. For both granular and EC formulations of ethoprop, HED believes the potential for post-application exposure is low because of limited contact with the soil. Therefore, a post-application dermal exposure assessment was not conducted.

<u>Restricted-Entry Interval (REI)</u>

The current product-label REI is 48 hours (72 hours in areas where rainfall is less than 25 inches per year). Under 40 CFR 156.208 (c) (2) (i), ai's classified as Acute toxicity category I for acute dermal, eye irritation or primary skin irritation are assigned a 48-hour REI. In addition, for organophosphates that may be applied outdoors in an area where the average annual rainfall for the site is less than 25 inches per year, the REI is 72 hours. Ethoprop is extremely acutely toxic. Ethoprop is classified as Toxicity Category I via the dermal route and was classified as Toxicity Category 1 for eye irritation, as well (with 0.1 ml resulting in 100% mortality).

No quantitative postapplication assessment is necessary for the registered uses of ethoprop. The interim REI based on the criteria laid out in 40 CFR 156.208 (c) (2) (i) meets the minimum requirements to be protective of potential post-application exposure.

[23] http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html
[24] http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219.

10.0 Incident Report

S. Recore et al., 12/02/14, D421955

One component of the Agency's registration review program is consideration of human observational information including incident data, medical case reports, general medical information, and epidemiology studies. In conjunction with a human health risk assessment based on other data sources, such human incident and other human data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

Based on the low frequency and severity of incident cases reported for ethoprop in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time with respect to incident cases that would warrant further investigation. Additionally, the findings of the research reviewed from the Agricultural Health Study do not support any changes to OPP's approach to quantitative risk assessment for ethoprop. However, OPP will continue to monitor the AHS and other epidemiologic results and will re-evaluate these conclusions as needed.

HED has prepared an ethoprop incident report review (S. Recore *et al*., 12/02/14, D421955, Ethoprop: Updated Tier I Review of Human Incidents for Preliminary Risk Assessment). The review considers a variety of types and sources of human observational information including human incident data, medical data/case report information, and epidemiological information in an effort to inform the re-evaluation of ethoprop in this phase of registration review. The human incident databases that were reviewed are:

- the OPP Incident Data System (IDS);
- NIOSH's Sentinel Event Notification System for Occupational Risks (SENSOR);

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Overall, there are few incidents involving ethoprop reported to IDS. Incidents in the IDS system include:

- For the Main IDS, from January 1, 2007 to August, 2014, there were 2 incidents reported for single chemical only in the database. There was one additional incident reported involving more than one chemical. These incidents were classified as moderate severity.
- In Aggregate IDS, from January 1, 2009 to August, 2014, there were 2 reported incidents involving ethoprop. These incidents were classified as minor severity.

The SENSOR-Pesticides database covers 11 states from 1998-2010, although reporting varies from state to state. Cases of pesticide-related illnesses are ascertained from a variety of sources, including: reports from local Poison Control Centers, state Department of Labor workers' compensation claims when reported by physicians, reports from State Departments of Agriculture, and physician reports to state Departments of Health. A query of SENSOR-Pesticides 1998-2010 identifies a total of nine cases, from five events, involving ethoprop. All nine cases experienced respiratory symptoms. Five cases experienced potential nervous system symptoms (mainly dizziness), and the moderate severity case also experienced potential cardiovascular symptoms.

In addition to the incident/poisoning data and medical case reports, epidemiological research can be an important source for human observational data and can potentially assist in identifying,

characterizing, and (ideally) quantifying linkages between human exposures and resulting health effects. For ethoprop, epidemiological data is available from the Agricultural Health Study (AHS). Across numerous evaluations of pesticide use in relation to different anatomical cancer endpoints, ethoprop was either not included or the statistical association was neither strong nor significant ($p>0.10$). Similarly, ethoprop use was either not measured or was not associated with the evaluations of non-cancer endpoints.

To date, there is one positive statistically significant association between ethoprop use and neurobehavioral performance. Starks et al. (2012) investigated neurobehavioral performance in relation to pesticide use in a sub-sample of male AHS participants (n=701). The purpose of this investigation was to examine associations between OP pesticide use and measures of neurobehavioral function in a large cohort of pesticide applicators with well characterized pesticide use histories. The primary hypothesis tested was whether long-term OP pesticide use was associated with adverse neurobehavioral (NB) outcomes. In this study, investigators evaluated the associations between (i) ever/never use based on any positive report at any interview and (ii) lifetime days of use based on the sum of lifetime days of use reported at each interview for each of 16 different organophosphate pesticides with performance on a series of 9 neurobehavioral tests, controlling for age, education, state and other neurological parameters which were selected from a list of 16 variables by using a stepwise selection process. From the analysis in which pesticide use is dichotomized as "ever/never use", authors reported significantly decreased ability to complete three (of the nine) neurobehavioral tasks that relate to motor speed, verbal learning and memory, and visual processing among those who reported ever use of ethoprop over the working lifetime. However, in the analysis where the pesticide use was set as the number of lifetime use days, only the association between the number of lifetime days using ethoprop and one NB task (motor speed and scanning) was significant. The authors conclude, overall, that they found "no consistent evidence of an association between OP use and adverse neurobehavioral performance tests among this older sample of pesticide applicators."

During the time frame that AHS conducted their analyses, OPP implemented a number of measures designed to reduce worker and environmental exposure as a result of ethoprop use. Subsequent to the 2001 IRED, all registered ethoprop labels (5481-9040 [formerly 264-452], 5481-9042 [formerly 264-469], and 5481-9041 [formerly 264-458]) were updated to reflect additional control measures. Important changes for granulars (5481-9040 & 5481-9042) implemented worker protections including enclosed cab, prohibition of certain applications (aerial, push-type spreaders, applications to peanuts, slit treatment, all hand applications) and lock and load (for 5481-9042). For the emulsifiable concentrate formulation of ethoprop, the changes included prohibition of certain application types (backpack, handwand, etc) and certain use sites (sugar cane). All ethoprop formulations increased restrictions on number of applications and the maximum application rates.

In summary, the available incident report details available incident and epidemiological data. The available incident data identified few incidents involving ethoprop that were reported to IDS or NIOSH SENSOR-Pesticides. The incidents involved cardiac, neurological, gastrointestinal, or respiratory symptoms. The available epidemiological data from the AHS do not support any changes to OPP's approach to quantitative risk assessment for ethoprop. OPP implemented significant worker exposure mitigations during the same time frame as the AHS epidemiological analyses were being conducted. OPP will continue to monitor incident data, the AHS and other epidemiologic results and will re-evaluate these conclusions as needed.

11.0 References

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Appendix A. Toxicology Profile

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for the food use for ethoprop are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21/28-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	
870.3465 90-Day Inhalation	yes	
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	CR	yes
870.6100b 90-Day Neurotoxicity (hen)	no	
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Develop. Neurotoxicity	CR	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	CR	yes
870.7800 Immunotoxicity	yes	yes
Special Studies Comparative Cholinesterase (rat)	-	yes

[1] The combined chronic toxicity/carcinogenicity study satisfies the requirement of the study.
[2] Subchronic 90-day and 6-month studies are available; therefore, a longer term study is not required.

A.2. Toxicity Profiles

Table A.2.1 Acute Toxicity Profile - Ethoprop

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral - Rat	00078035	M LD_{50} = 56.2 mg/kg F LD_{50} = 30.2 mg/kg	I
870.1100	Acute oral – Rat	44472501	F LD_{50} = 56 mg/kg	II
870.1200	Acute dermal – Rabbit (technical form)	00078035	LD_{50} = 25.74 mg/kg	I
870.1200	Acute dermal – Rabbit (technical form)	42979502	M LD_{50} = 7.9 mg/kg F LD_{50} = 9.3 mg/kg	I
870.1200	Acute dermal – Rat (technical form)	42979501	M LD_{50} = 1280 mg/kg F LD_{50} = 424 mg/kg	II
870.1200	Acute dermal – Rabbit (20% granular form)	00132267	M LD_{50} = 45.5 mg/kg F LD_{50} = 31.4 mg/kg	I
870.1300	Acute inhalation -Rat	070060	LC_{50} = 0.123 mg/L	II
870.2400	Acute eye irritation - Rabbit	00078036	0.1 mL resulted in 100% mortality	-
870.2500	Acute dermal irritation - Rabbit	00048774	0.5 mL resulted in 100% mortality	-
870.2600	Skin sensitization – guinea pig	N/A[1]	N/A	N/A

[1]Requirement for dermal sensitization study waived in 1987 Registration Standard due to high acute dermal toxicity.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3050	28-Day oral toxicity rodents Crl:CD(SD)IGS BR	45388501 (2001) acceptable/nonguideline 0, 0.2, 0.5, 1.0 ppm M 0,0.018, 0.045, 0.090 mg/kg/day F 0, 0.021, 0.052, 0.099 mg/kg/day	Systemic NOAEL = 0.09/0.099 (M/F). Systemic LOAEL = not identified. RBC AChE inhibition NOAEL = 0.09/0.099 (M/F). RBC AChE inhibition LOAEL = not identified.
870.3050	28-Day oral toxicity rodents Crl:CD(SD)IGS BR	45388502 (2001) acceptable/nonguideline 0, 7.5, 15, 30 ppm M: 0, 0.567, 1.159, 2.363 mg/kg/day F: 0, 0.707, 1.366, 2.677 mg/kg/day	Systemic NOAEL = 2.363/2.677 (M/F) mg/kg/day). Systemic LOAEL = not identified. LOAEL for erythrocyte cholinesterase inhibition = 7.5 ppm (-22%; 0.567 mg/kg/day) in males and 30 ppm (-40%; 2.677 mg/kg/day) in females). NOAEL for erythrocyte cholinesterase inhibition was not established in males and is 15 ppm (1.366 mg/kg/day) in females.
870.3150	90-Day oral toxicity in nonrodents	00075240 (1967) acceptable/guideline 0, 1, 3, 100 ppm 0, 0.025, 0.075, 2.5 mg/kg/day	RBC AChE inhibition NOAEL = 0.075 mg/kg/day RBC AChE inhibition LOAEL = 2.5 mg/kg/day Note: Brain AChE not measured. Old DER. Only 3 dogs/group.
870.3200	21-Day dermal toxicity rabbits **TECHNICAL**	MRID 41304404 (1989) 0.03, 0.1, 1 mg/kg/day	Brain and RBC AChE inhibition LOAEL = 1 mg/kg/day Brain and RBC AChE inhibition NOAEL = 0.1 mg/kg/day
870.3200	21-Day dermal toxicity rats **TECHNICAL**	45074602 (1990) 0.3, 1, 10 mg/kg/day	RBC AChE inhibition LOAEL = 1 mg/kg/day RBC AChE inhibition NOAEL = 0.3 mg/kg/day Brain AChE inhibition LOAEL = 10 mg/kg/day Brain AChE inhibition NOAEL = 1 mg/kg/day

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	28-Day dermal toxicity rat **GRANULAR FORMULATION** **19.34%**	45034801 (2000) 0, 100, 500, or 2000 mg/kg/day [0, 19.34, 96.7, 387 mg/kg/day (corrected for % a.i.)]	RBC AChE inhibition LOAEL = 19.34 mg/kg/day (♂) RBC AChE inhibition NOAEL = not identified (♂) RBC AChE inhibition LOAEL = 96.7 mg/kg/day (♀) RBC AChE inhibition NOAEL = 19.34 (♀) Brain AChE inhibition LOAEL = 96.7 mg/kg/day (♂/♀) Brain AChE inhibition NOAEL = 19.34 mg/kg/day (♂/♀)
870.3465	4-Week inhalation toxicity rat Technical	48779601 (2012) 0, 0.498, 2.05, & 6.36 µg/L	RBC AChE inhibition LOAEL = 0.498 µg/L (♂/♀) RBC AChE inhibition NOAEL = not identified ♂/♀) Brain AChE inhibition LOAEL = 2.05 µg/L (♂/♀) Brain AChE inhibition NOAEL = 0.498 µg/L (♂/♀)
870.3700a	Prenatal developmental in rodents	41304402 (1989) MATERNAL 2, 9, 18 mg/kg/day	maternal NOAEL = 2 mg/kg/day maternal LOAEL = 9 mg/kg/day based on decreased body weight gain and increased incidence of soft stool. developmental toxicity NOAEL was ≥ 18 mg/kg/day, the highest dose tested.
870.3700b	Prenatal developmental in rabbits	41304403 (1989) MATERNAL 0.625, 1.25, 2.5 mg/kg/day	maternal and developmental NOAELs were ≥ 2.5 mg/kg/day, the highest dose tested.
870.3800	Reproduction and fertility effects	MRID 41921201 (1991) PARENTAL	parental LOAEL for systemic toxicity = 13 mg/kg/day, based on decreased body weights. parental NOAEL for systemic toxicity = 2.3

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
	rats	0, 1, 30, 300/150 ppm 0.08, 2.3, 24/13 mkd. ↓dose: excess mortality in F1a pups.	mg/kg/day parental LOAEL for brain cholinesterase inhibition = 2.3 mg/kg/day. parental NOAEL for brain cholinesterase inhibition = 0.08 mg/kg/day parental NOAEL for red blood cell cholinesterase inhibition ≥ 13 mg/kg/day, the highest dose tested. offspring LOAEL = 13 mg/kg/day, based on body weight decrement. offspring NOAEL = 2.3 mg/kg/day
870.4100b	Chronic toxicity dogs COMBINED 1-YEAR + 5 MONTH DOG	00160179, 41498601 (1986, 1990) M: 0, 0.01, 0.025, 1.0, 10.0 mg/kg/day F: 0, 0.01, 0.025, 1.0, 10.0 mg/kg/day	RBC AChE inhibition LOAEL = 1 mg/kg/day RBC AChE inhibition NOAEL = 0.025 mg/kg/day Brain AChE inhibition LOAEL = 10 mg/kg/day Brain AChE inhibition NOAEL = 1 mg/kg/day Systemic LOAEL = 1.0 mg/kg/day, based on decreases in red blood cell parameters in males and females and elevations in SGPT in males. Systemic LOAEL = 0.025 mg/kg/day
870.4200a	Chronic toxicity/ Carcinogenicity rat Crl:CD	42530201 (1992) M: 0, 1, 60, 600/400 ppm 0.04, 2.44, 18.38 mkd. ↓dose: signs, death, major ↓BW in 1st 2 wks. F: 0, 1, 60, 600/400 ppm 0, 0.06, 3.56, 23.98	Systemic LOAEL = 400 ppm (18.38 mg/kg/day in males and 23.98 mg/kg/day in females), based on reduced body weight gain, reduced food consumption, reduced erythrocyte count, reduced hemoglobin, and reduced hematocrit. Systemic NOAEL = 60 ppm (2.44 mg/kg/day in males and 3.56 mg/kg/day in females) LOAEL for red blood cell and brain cholinesterase inhibition = 60 ppm (2.44 mg/kg/day in males and 3.56 mg/kg/day in females).

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			NOAEL for red blood cell and brain cholinesterase inhibition = 1 ppm (0.04 mg/kg/day in males and 0.06 mg/kg/day in females)
870.4200b	Carcinogenicity mice	40356301, 43326001 M: 0, 0.2, 2, 30 ppm 0, 0.026, 0.254, 3.96 mg/kg/day F: 0, 0.2, 2, 30 ppm 0, 0.032, 0.318, 4.9 mg/kg/day	Systemic LOAEL = 3.96 mg/kg/day (♂) and 4.91 mg/kg/day (♀)based on body weight and body weight gain decreases. Systemic NOAEL = 0.254 (♂),0.318 (♀)
870.6100b	Delayed Neurotoxicity Study Hen	40609401 6.5 mg/kg initially, followed by a second oral dose 5.3 mg/kg 21-days later.	no clinical signs or neurohistopathology.
870.6200a	Acute Neurotoxicity Rat (Oral gavage) Crl:CD BR VAF/Plus	43197701 (1994) M: 0, 5, 50, 75 mg/kg F: 0, 5, 25, 50 mg/kg tested blood AChE on day 2, brain on day 15	neurotoxicity LOAEL = 25 mg/kg, based on neurobehavioral signs (salivation, lip smacking, ataxia, negative pupillary response and/or tremors) in females related to cholinesterase inhibition. neurotoxicity NOAEL = 5 mg/kg. LOAEL inhibition RBC cholinesterase = 5 mg/kg (♂) NOAELinhibition RBC cholinesterase = <5 mg/kg (♂) Note: no inhibition of brain AChE observed
870.6200a	Acute Neurotoxicity - Rat time course	43442402 (1994) males: 0, 30 or 60 mg/kg target; 0, 24.2 or 52 mg/kg actual; females: 0, 20 or 40 mg/kg target; 0, 15.7 or 33 mg/kg actual.	AChE inhibition NOAEL = not identified. AChE inhibition LOAEL ≤15.7 mg/kg (20 mg/kg dose), based on inhibition of plasma, RBC and brain AChE in females. Neurotoxicity NOAEL = 15.7 mg/kg .

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			Neurotoxicity LOAEL =33 mg/kg, based on cholinergic symptoms (tremors, excessive salivation) in females.
870.6200b	Subchronic Neurotoxicity Rat (Oral dietary)	43442401 (1994) 0, 4, 40 or 400 ppm (0, 0.260, 2.648 or 27.113 mg/kg/day for males and 0, 0.306, 2.989 or 31.311 mg/kg/day for females, respectively	Systemic/neurotoxicity NOAEL = 40 ppm (2.648 mg/kg/day). Systemic/neurotoxicity LOAEL = 400 ppm (27.113 mg/kg/day) based on decreased body weight gain/food consumption, decreased hindlimb grip strength, motor activity and analgesic response time in males, and possible cholinergic signs. RBC AChE inhibition NOAEL = 4 ppm (♂/♀) . RBC AChE inhibition LOAEL = 40 ppm (♂/♀). Brain AChE inhibition NOAEL = not identified (♀) . Brain AChE inhibition LOAEL = 4 ppm (♀).
870.6300	Developmental Neurotoxicity – Main Study Rat (Oral gavage)	46364801 (2004) 0, 3, 30 and 180 ppm from GD6 - LD21. Average doses to the animals were 0, 0.3, 2.8 and 16.6 mg/kg/day during gestation and 0, 0.7, 6.2 and 38.2 mg/kg/day during lactation for the 0, 3, 30 and 180 ppm groups, respectively.	maternal LOAEL for systemic toxicity = 180 ppm (38.2 mg/kg/day during lactation) based on clinical signs (coarse tremors, repetitive chewing, muscle fasciculations, and nasal stains) and decreased body weight and body weight gain during lactation. maternal NOAELfor systemic toxicity = 30 ppm (6.2 mg/kg/day during lactation). maternal LOAEL for plasma AChE and RBC AChE inhibition = 3 ppm (0.7 mg/kg/day during lactation based on enzyme inhibition on LD 21. T maternal NOAEL for plasma AChE and RBC AChE inhibition was not established. maternal LOAEL for brain AChE inhibition for Ethoprop = 30 ppm (6.2 mg/kg/day during

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			lactation) based on enzyme inhibition on LD 21. maternal NOAEL for brain AChE inhibition = 3 ppm (0.7 mg/kg/day during lactation). offspring LOAEL for systemic toxicity = not identified. offspring NOAEL for systemic toxicity = 180 ppm (38.2 mg/kg/day during lactation). offspring LOAEL for RBC AChE inhibition = 180 ppm (38.2 mg/kg/day during lactation, respectively) based on enzyme inhibition on PND21. offspring NOAEL for RBC AChE inhibition = 30 ppm (6.2 mg/kg/day during lactation). offspring LOAEL for plasma AChE and brain AChE inhibition = 30 ppm (6.2 mg/kg/day during lactation) based on enzyme inhibition on PND21. offspring NOAEL for plasma AChE and brain AChE inhibition = 3 ppm (0.7 mg/kg/day during lactation).
870.6300	Developmental Neurotoxicity – Range Finding Rat (Oral gavage)	46364802 (2004) 0, 3, 30 or 240 ppm from GD 6 - GD 20 (inclusive). Mean intake based on average consumption during gestation weeks 2 and 3 was 0, 0.3, 2.5 and 21.4 mg/kg/day at 0, 3, 30 and 240 ppm, respectively.	maternal LOAEL for RBC and brain AChE activity = 30 ppm. The maternal NOAEL for RBC and brain AChE activity was 3 ppm. fetal LOAEL = 240 ppm based on inhibition of plasma AChE and RBC AChE activity. fetal NOAEL = 30 ppm.
870.7485	Metabolism and pharmacokinetics	41804301 acceptable	Ethoprop was administered to Crl:CD(SD)BR rats as a single IV bolus (males and females); single oral bolus (females, metabolism and pharmacokinetic studies; males, metabolism only); or by multiple oral doses. Following oral administration, ethoprop was completely

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
			absorbed and completely metabolized. Excretion was by urinary (≥50% administered dose), fecal (7-16%), and respiratory (11-19%) routes and was essentially complete by 48 hours. Terminal elimination $t_{1/2}$ in blood was 92-135 hours. Metabolism was by dealkylation of one or both S-propyl groups, followed by hydroxylation and probably conjugation. Two urinary metabolites were identified by HPLC while 3 others were believed to be possible conjugates of those metabolites. The TLC profiles of fecal metabolites were similar to the profiles for urinary metabolites.
870.7800	Immunotoxicity male Sprague-Dawley (Crl:CD(SD)) rats	48632501 acceptable dietary: 0, 5, 15, or 30 ppm (equivalent to 0.4, 1.2, or 2.43 mg/kg/day, respectively) for 4 weeks.	systemic toxicity LOAEL = 5 ppm (0.4 mg/kg/day) based on reduced red blood cell cholinesterase activity systemic toxicity NOAEL =< 0.4 mg/kg/day. immunotoxicity NOAEL = 30 ppm (equivalent to 2.43 mg/kg/day), the highest tested dose.
Non-guideline	Acute Comparative Cholinesterase - Rat	46278701 (2004) administered to 6 adult rats/sex/dose at dose levels of 0, 0.5, 1, 2, and 4 mg/kg and to 10 rat pups/sex/dose at dose levels of 0, 0.5, 1, and 2 mg/kg.	adult LOAEL for erythrocyte cholinesterase inhibition = 2 mg/kg (-22% inhibition in males), adult NOAEL for erythrocyte cholinesterase inhibition = 1 mg/kg. pup LOAEL for erythrocyte cholinesterase inhibition = 1 mg/kg (-17% in males) pup NOAEL for erythrocyte cholinesterase inhibition = 0.5 mg/kg. adults NOAEL for brain cholinesterase inhibition = 4 mg/kg, the highest dose tested. pup LOAEL for brain cholinesterase inhibition = 1 mg/kg (-10% in both males and females), pup NOAEL for brain cholinesterase inhibition = 0.5 mg/kg.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile - Ethoprop			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Non-guideline	Repeat-dosing Comparative Cholinesterase - Rat	46636401 (2005) administered to 6 young adult Wistar rats (8-10 weeks old)/sex/group and to 10 Wistar preweanling rat pups (11 days old)/sex/group for 11 consecutive days. Nominal doses for adults were 0, 0.25, 0.5, or 1 mg/kg/day and for pups were 0, 0.25, 0.5, or 1 mg/kg/day.	In **adults**, the **LOAEL for plasma cholinesterase inhibition** was 0.5 mg/kg/day (-44% in females), the lowest dose tested. The NOAEL in adults was <0.5 mg/kg/day. In **pups**, the LOAEL for plasma cholinesterase inhibition was 0.25 mg/kg/day (-24% in females), the lowest dose tested. The NOAEL in pups was <0.25 mg/kg/day. In **adults**, the **LOAEL for erythrocyte cholinesterase inhibition** was 1 mg/kg/day (-53% in males and -28% in females), with a NOAEL of 0.5 mg/kg/day. In **pups**, the LOAEL for erythrocyte cholinesterase inhibition was 0.5 mg/kg/day (-39% in males), with a NOAEL of 0.25 mg/kg/day. In **adults**, the **LOAEL for brain cholinesterase inhibition** was 2 mg/kg/day (-12% in females), with a NOAEL of 1 mg/kg/day. In **pups**, the LOAEL for brain cholinesterase inhibition was 0.25 mg/kg/day (-10% in males and -15% in females), the lowest dose tested. The NOAEL was <0.25 mg/kg/day.

Appendix A3. Summary of Occupational and Residential BMDL10 Values Adjusted for Toxicity Duration and Breathing Rates.

Table A3. Ethoprop inhalation BMDL10 values adjusted for toxicity duration and specific breathing rates for various exposure scenarios

Population	**Scenario**	**Toxicity Duration Adjustment**		**$BMDL_{10}$ (mg/L or mg/m^3)**	**$BMDL_{10}$ (mg/kg/day; breathing rate specific)**		
		hr/day	**day/wk**		**8.3 L/min**	**16.7 L/min**	**29 L/min**
Occupational	Handler	8	5	0.000825 mg/L	0.035 mg/kg/day	0.071 mg/kg/day	0.123 mg/kg/day
Residential	Handler	NA	NA	NA	NA	NA	NA
	Outdoor post-applic	NA	NA	0.825 mg/m^3	NA	NA	NA
	Indoor post-applic	NA	NA	NA	NA	NA	NA
	Bystander	24	7	0.147 mg/m^3	NA	NA	NA

NA = not applicable

Appendix B. Summary of OPP's Cholinesterase Policy & Use of BMD Modeling

OPP's AChE policy (USEPA, 2000[25]) describes the manner in which AChE data are used in human health risk assessment. The following text provides a brief summary of that document to provide context to points of departure selected.

AChE inhibition can be inhibited in the central or peripheral nervous tissue. Measurements of AChE or AChE inhibition in peripheral tissues (e.g., liver, diaphragm, heart, lung, etc.) are rare. As such, experimental laboratory studies generally measure brain (central) and blood (plasma and red blood cell, RBC) AChE. Blood measures do not represent the target tissue, *per se*, but are instead used as surrogate measures for peripheral toxicity in studies with laboratory animals or for peripheral and/or central toxicity in humans. In addition, RBC measures represent AChE, whereas plasma measures are predominately butyryl-AChE (BuChE). Thus, RBC AChE data may provide a better representation of the inhibition in target tissues. As part of the dose response assessment, evaluations of neurobehavior and clinical signs are performed to consider the dose response linkage between AChE inhibition and apical outcomes.

Refinements to OPP's use of AChE data have come in the implementation of BMD approaches in dose response assessment. Beginning with the OP CRA, OPP has increased its use of BMD modeling to derive PODs for AChE inhibiting compounds. Most often the decreasing exponential empirical model has been used.

OPP does have not a defined BMR for OPs. However, the 10% level has been used in the majority of dose response analyses conducted to date. This 10% level represents a 10% reduction in AChE activity (i.e., inhibition) compared to background (i.e., controls). Specifically, the BMD_{10} is the estimated dose where AChE is inhibited by 10% compared to background. The $BMDL_{10}$ is the lower confidence bound on the BMD_{10}.

The use of the 10% BMR is derived from a combination of statistical and biological considerations. A power analysis was conducted by EPA's Office of Research and Development on over 100 brain AChE datasets across more than 25 OPs as part of the OP CRA (USEPA, 2002). This analysis demonstrated that 10% is a level that can be reliably measured in the majority of rat toxicity studies. In addition, the 10% level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in AChE activity in the brain compartment and is a response level close to the background brain AChE level. With respect to biological considerations, a change in 10% brain AChE inhibition is protective for downstream clinical signs and apical neurotoxic outcomes. With respect to RBC AChE inhibition, these data tend to be more variable than brain AChE data. OPP begins its BMD analyses using the 10% BMR for RBC AChE inhibition but BMRs up to 20% could be considered on a case-by-case basis as long as such PODs are protective for brain AChE inhibition, potential peripheral inhibition, and clinical signs of neurotoxicity.

[25] USEPA (2000) Office of Pesticide Programs, US Environmental Protection Agency, Washington DC 20460. August 18, 2000 Office of Pesticide Programs Science Policy of The Use of Data on Cholinesterase Inhibition for Risk Assessments of Organophosphorous and Carbamate Pesticides.

Appendix C. Summary Tables of Benchmark Dose (BMD) Analyses

Toxicity studies with AChE data were analyzed using the most recent version of EPA's Benchmark Dose Software (Version 2.4). Full results and technical details for these analyses can be found in the latest BMD memo (J. Liccione; 09-15-2015; TXR 0057238).

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)
MRID 46278701 CCA Acute Study- Single Dose	Female Adult	Brain	no dose response	
	Male Adult	Brain	no dose response	
MRID 46278701 CCA Acute Study- Single Dose	Female Adult	RBC	1.09451	0.719828
	Male Adult	RBC	0.649245	0.468507
MRID 46278701 CCA Acute Study- Single Dose	Female PND11	Brain	0.817231	0.624816
	Male PND11	Brain	0.961856	0.642672
MRID 46278701 CCA Acute Study- Single Dose	Female PND11	RBC	0.5498	0.4187
	Male PND11	RBC	0.570495	0.440426

Appendix Table 2.2 BMD results of repeated dosing studies ranging in duration from 11 to 37 days.

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
MRID 46636401 CCA Repeat Study- 11 days	Female Adult	Brain	no dose response	
	Male Adult	Brain	no dose response	
MRID 46636401 CCA Repeat Study- 11 days	Female Adult	RBC	0.247409	0.190533
	Male Adult	RBC	0.552759	0.382568
MRID 46636401 CCA Repeat Study- 11 days	Female PND11	Brain	0.150686	0.116861
	Male	Brain	0.18691	0.160026

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg/day)	**$BMDL_{10}$ (mg/kg/day)**
	PND11			
MRID 46636401 CCA Repeat Study- 11 days	Female PND11	RBC	0.1536	0.1082
	Male PND11	RBC	0.105645	0.065269
MRID 46364802 RF DNT Study – 14 days	Dams	Brain	2.41108	1.84917
	Dams	RBC	0.163555	0.128748
MRID 46364802 RF DNT Study – 14 days	GD20 fetus	Brain	no adequate fit	no adequate fit
	GD20 fetus	RBC	5.46166	1.86428
MRID 45388502 28-day rat toxicity study	Female Adult	Brain	not measured	
	Male Adult	Brain	not measured	
MRID 45388502 28-day rat toxicity study	Female Adult	RBC	0.453912	0.349179
	Male Adult	RBC	0.237535	0.207944
MRID 46364801 Main DNT Study – 37 days	Dams	Brain	5.01245	1.57613
MRID 46364801 Main DNT Study – 37 days	Dams	RBC	0.251676	0.22383
MRID 46364801 Main DNT Study – 37 days	Female PND21 pups	Brain	8.75985	6.40739
	Male PND21 pups	Brain	5.46684	4.32517

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
MRID 46364801 Main DNT Study – 37 days	Female PND21 pups	RBC	2.96579	1.88126
	Male PND21 pups	RBC	4.41733	2.52439

Appendix Table 2.2 BMD results of repeated exposure studies via the dermal and inhalation routes.

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10}	$BMDL_{10}$
MRID 45074602 21-Day Dermal Toxicity – Rats Technical (liquid)	Female	Brain	0.4406	0.1942
	Male	Brain	no reliable fits	
MRID 45074602 21-Day Dermal Toxicity – Rats Technical (liquid)	Female	RBC	0.274287	0.214247
	Male	RBC	0.4047	0.2702
MRID 41304404 21-Day Dermal Toxicity – Rabbits Technical (liquid)	Female	Brain	0.901831	0.163516
	Male	Brain	0.142702	0.115131
MRID 441304404 21-Day Dermal Toxicity – Rabbits Technical (liquid)	Female	RBC	0.2035	0.1625
	Male	RBC	no reliable fits	
MRID 45034801 28-Day Dermal Toxicity – Rats	Female	Brain	no reliable fits	
	Male	Brain	no reliable fits	

Ethoprop/Study	Sex/age	Compartment	BMD Results	
			BMD_{10}	$BMDL_{10}$
Granular formulation (19.34% a.i.)				
MRID 45034801 28-Day Dermal Toxicity – Rats Granular formulation (19.34% a.i.)	Female	RBC	15.7	10.4
	Male	RBC	14.8	11.1
MRID 48779601 4-Week Inhalation Toxicity – Rats Technical	Female	Brain	1.5988	1.46858
	Male	Brain	1.98637	1.38417
MRID 48779601 4-Week Inhalation Toxicity – Rats Technical	Female	RBC	2.42513	1.30211
	Male	RBC	1.296	0.8245

Appendix D. Physical/Chemical Properties

Table D.1 Physicochemical Properties of Technical Grade Ethoprop.		
Parameter	Value	Reference
Boiling point	86-91ºC at 0.2 mmHg	Ethoprop Registration Standard (10/20/87)
pH	6.65 in saturated aqueous solution at 21ºC	
Density	1.097 g/mL at 15ºC	
Water solubility	843 ppm at 21ºC	
Solvent solubility	Completely miscible in hexane, xylene, acetone, and ethanol	
Vapor pressure	3.89×10^{-4} Torr at 24ºC	
Dissociation constant, pK_a	not available	
Octanol/water partition coefficient, $Log(K_{OW})$	3.59 at 21ºC	
UV/visible absorption spectrum	not available	

Appendix E. International Residue Limits

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US	Canada		Mexico[2]	Codex[3]
§ 180.262 (a) General. (1) ethoprop, O-ethyl S,S-dipropyl phosphorodithioate	O-ethyl S,S-dipropyl phosphorodithioate			ethoprophos
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex[3]
Banana	0.02	0.02		0.02
Bean, lima	0.02	0.09 (edible-podded)		
Bean, snap, succulent	0.02	0.09		
Cabbage	0.02	0.02		
Corn, field, forage	0.02			
Corn, field, grain	0.02	0.02		
Corn, field, stover	0.02			
Corn, sweet, forage	0.02			
Corn, sweet, kernel plus cob with husks removed	0.02	0.02		
Corn, sweet, stover	0.02			
Cucumber	0.02	0.02		0.01
Hop, dried cones	0.02	0.02		
Peppermint, tops	0.02	0.02		
Pineapple[1]	0.02			
Potato	0.02	0.02		0.05
Spearmint, tops	0.02	0.02		
Sugarcane, cane	0.02	0.02		0.02
Sweet potato, roots	0.02	0.02		0.05 sweet potato
MRLs with No US Equivalent				
Edible offal (mammalian)				0.01 (*)
Meat (from mammals other than marine mammals)				0.01 (*)
Melons, except watermelon				0.02
Milks				0.01 (*)
Peppers chili, dried				0.2
Peppers, sweet (including pimento or pimiento)				0.05
Strawberry				0.02 (*)
Sugar cane fodder				0.02 (*)
Tomato				0.01 (*)
Turnip, garden				0.02 (*)
Completed: M. Negussie; 07/29/2015				

[1]There are no U.S. registrations as of July 23, 2009, except for existing stocks bearing old labeling whose sale, distribution, and use is allowed, provided it is consistent with the terms of the cancellation order of July 9, 2009; i.e., the EPA will allow the technical registrant to continue to sell and distribute existing stocks of the amended registered product bearing old labeling for use on pineapple for 18 months (until January 9, 2011) and persons other than the registrant may continue to sell and/or use existing stocks of product bearing the old labeling until such stocks are exhausted, provided that such use is consistent with the terms of the previously approved labeling on, or that accompanied, the modified product.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation